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# **MASTERS DEGREE: The Impact of a Diabetes Management Team on the Metabolic Control and Prevalence of Complications in Paediatric Patients with Type 1 Diabetes Mellitus**

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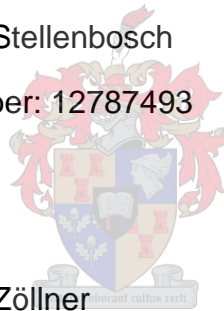
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# PLAGIARISM DECLARATION

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## DECLARATION

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I, Dr Kajee (author) have conceptualised and designed this study with the assistance and support of my supervisor, Dr Zöllner. I have also acquired the data. Statistical analysis of the data was performed by a University of Stellenbosch statistician, Mr Justin Harvey. Interpretation of the statistical analysis was done by me, with the aid of my supervisor. He also assisted with corrections which I completed prior to submission of this thesis.

**FINANCIAL DISCLOSURE:** I have no financial relationships relevant to this thesis to disclose.

**FUNDING:** No funding was received for completion of this thesis.

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## ABSTRACT

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**BACKGROUND:** In various centres a diabetes management team (DMT) was found to have an impact on glycaemic control.

**HYPOTHESIS:** A DMT improves HbA1c levels, decreases the diabetic ketoacidosis (DKA) and recurrent DKA (rDKA) rates, reduces admissions, shortens the length of hospital stay, improves clinic attendance rate, leads to a reduced dose of insulin per patient, facilitates the use of an intensive insulin regimen and decreases the prevalence of complications of type 1 diabetic (T1DM) paediatric and adolescent patients attending Tygerberg Children's Hospital (TCH).

**STUDY DESIGN:** Retrospective cohort study (a time series) with cross-sectional elements.

**METHODS:** 190 T1DM patients attending the paediatric diabetic clinic at TCH between August 2004 and July 2011 were reviewed. Data extracted: HbA1c levels, DKA and rDKA admissions, total number of admissions, length of hospital stay, clinic attendances, insulin regimen and dose, and complications. 4 time periods were compared: P1 (paediatric endocrinologist only), P2 (introduction of DMT after a period when no paediatric endocrinologist was available), P3 [introduction of diabetes nurse educator (DNE)], and P4 (substitution of DNE).

**RESULTS:** HbA1c increased from 9% (95% CI 7.85-10.15) in P1 to 10.9% (95% CI 9.6-12.2) in P2, and decreased to 9.25% (95% CI 8.75-9.75) in P4 ( $p=0.01818$ ). DKA rate improved from 32.5 (P1) to 23.5 /100 patient years (P4). Recurrent DKA rate improved from 18.8% (P1) to 9.6% (P4). Admissions decreased from 0.79 (95% CI 0.46-1.12) in P1 to 0.18 (95% CI 0.02-0.34) in P4 ( $p=0.00127$ ). Patients hospitalised for longer than 30 days decreased from 30% (P2) to 15.1 % (P4). Number of insulin injections increased from 2.97 (95% CI 2.91-3.03) in P1, to 3.06 (95% CI 2.97-3.14) in P2 but remained constant thereafter ( $p=0.0015$ ). Few complications were documented in P1. Prevalence of microalbuminuria was similar (95% CI 26.9-46.2%) in all periods, as was retinopathy (95% CI 10.3-13.3%). Prevalence of limited joint mobility (LJM) increased from 26% (P2) to 42.9% (P4). Levels of triglycerides were similar in all periods, low-density lipoprotein cholesterol (LDLC) decreased to 2.6mmol/l (95% CI 2.38-2.81) in P3 and high-density lipoprotein cholesterol (HDLC) decreased to 1.38mmol/l (95% CI 1.27-1.49) in P4.

CONCLUSIONS: After introduction of the full DMT (including the DNE), HbA1c decreased and showed less variation, DKA and rDKA rate decreased, hospital stay shortened, number of insulin injections/day increased and complications were more readily identified. Decreased clinic attendance corresponded to poorer glycaemic control and the period where inexperienced personnel were responsible for diabetes care. There was an increase in usage of both the modified conventional regimen as well as the basal bolus regimen as time progressed. It is therefore recommended that the services of the DMT, which includes a DNE, should continue.

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## OPSOMMING

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**AGTERGROND:** Verskeie sentrums het vantevore bevind dat 'n diabetiese bestuursplan (DBS) 'n impak op glukemiese beheer het.

**HIPOTESE:** 'n DBS verlaag HbA1c vlakke, verminder diabetiese ketoasidose (DKA) en herhalende DKA (hDKA) episodes, verminder hospitaal toelatings, verkort hospitaal verblyf, verbeter kliniek bywoning, lei tot 'n verminderde dosis insulien gebruik per pasiënt, fasiliteer die gebruik van 'n intensiewe insulien skedule en, verminder die voorkoms van komplikasies van tipe 1-diabetes (T1DM) in pediatriese en adolessente pasiënte wat Tygerberg Kinder Hospitaal (TKH) besoek.

**STUDIE-ONTWERP:** Terugwerkende Kohort studie ('n tyd reeks) met deursnee-elemente.

**METODE:** Die bywoning van 190 T1DM pasiënte by die pediatriese diabetese kliniek by TKH tussen Augustus 2004 en Julie 2011 is nagegaan. Die volgende data is versamel: HbA1c vlakke, DKA en hDKA opnames, die totale aantal opnames, die lengte van hospitaal verblyf, kliniek bywoning, insulien skedule, insulien dosis, en komplikasies. Vier tydperke is met mekaar vergelyk: P1 (net pediatriese endokrinoloog), P2 (bekendstelling van DBS na 'n periode waar daar geen pediatriese endokrinoloog was nie), P3 [bekendstelling van diabetiese verpleegster opvoeder (DVO)], en P4 (vervanging van DVO).

**RESULTATE:** HbA1c het toegeneem van 9% (95% CI 7,85-10,15) in P1 tot 10,9% (95% CI 9,6-12,2) in P2, en het verminder na 9,25% (95% CI 8,75-9,75) in P4 ( $p = 0,01818$ ). DKA voorkoms het verbeter van 32,5 (P1) na 23,5 / 100 pasiënt jare (P4). HDKA het verbeter van 18,8% (P1) tot 9,6% (P4). Toelatings het afgeneem van 0,79 (95% CI 0,46-1,12) in P1 tot 0,18 (95% CI 0,02-0,34) in P4 ( $p = 0,00127$ ). Die aantal pasiënte wat gehospitaaliseer was vir langer as 30 dae het verminder van 30% (P2) na 15,1% (P4). Die hoeveelheid insulien inspuitings het toegeneem van 2,97 (95% CI 2,91-3,03) in P1, na 3,06 (95% CI 2,97-3,14) in P2, maar het daarna konstant gebly ( $p=0,0015$ ). Min komplikasies is gedokumenteer vir P1. Die voorkoms van mikroalbuminurie was soortgelyk (95% CI 26,9-46,2%) in al die tydperke, asook retinopatie (95% CI 10,3-13,3%). Voorkoms van beperkte gewrigsmobiliteit het verhoog vanaf 26% (P2) na 42,9% (P4). Vlakke van trigliseriede was soortgelyk in al die tydperke, lae-digtheid lipoproteïen cholesterol het afgeneem na 2,6mmol / l (95%

CI 2,38-2,81) in P3 en hoë-digtheid lipoproteïen cholesterol het afgeneem na 1.38mmol / l (95% CI 1,27-1,49) in P4.

GEVOLGTREKKING: Na bekendstelling van die volle DBS (insluitend die DVO), het HbA1c verlaag en meer konstant vertoon, DKA en hDKA syfers het gedaal, hospitaal verblyf het verkort, die hoeveelheid van insulieninspuitings per dag het verhoog en komplikasies is makliker geïdentifiseer. Verminderde kliniek bywonings korrespondeer met slegte glukemiese beheer en met die periode waar onervare personeel verantwoordelik was vir diabetiese sorg. Daar was 'n toeneming in die gebruik van albei die gemodifiseerde konvensionele regimen en die basale bolus regimen. Ons beveel dus aan dat die dienste van die DBS, insluitend 'n DVO moet voortgaan.

## ACKNOWLEDGEMENTS

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The successful completion of this study would not have been possible without the assistance and support of the following people:

My supervisor Dr E Zöllner provided invaluable assistance, support and encouragement, without which this study would not have been possible. Throughout the course of completing this study, he has shown great patience and understanding.

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I would like to express my sincere gratitude to my parents for their encouragement academically, my husband Mikaeel who looked after our newborn while I sat for hours at the computer, and my brothers Yaseen and Riyaadh who assisted with thesis advice and development of my computer skills; as well as friends for their support throughout this study. Without their encouragement, the difficulties of this study would have been an overwhelming experience.



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## LIST OF ABBREVIATIONS

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Anti-GAD	anti-glutamic acid decarboxylase
BMI	body mass index
CV	coefficient of variation
DBS	diabetiese bestuursplan
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis/diabetiese ketoasidose
DMT	diabetes management team
DNE	diabetic nurse educator
DVO	diabetiese verpleegster opvoeder
EDIC	Epidemiology of Diabetes Interventions and Complications
GEE	generalised estimating equations
HbA1c	glycosylated haemoglobin
hDKA	herhalende diabetiese ketoasidose
HDLC	high-density lipoprotein cholesterol
IA2	islet antigen 2
ISPAD	International Society for Paediatric and Adolescent Diabetes
LDLC	low-density lipoprotein cholesterol
LJM	limited joint mobility
MIDAC	Microalbuminuria in Diabetic Adolescents and Children
NGSP	National Glucose Standardisation Program
P1	period 1
P2	period 2
P3	period 3

P4	period 4
Rdka	recurrent diabetic ketoacidosis
SE	standard error
TCH	Tygerberg Children's Hospital
T1DM	type 1 diabetic/tipe 1 diabetes
TG	triglycerides
TKH	Tygerberg Kinder Hospitaal
TSC	total serum cholesterol
UAC	urine albumin to creatinine ratio

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# 1 INTRODUCTION

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Type 1 diabetes mellitus is amongst the most frequent chronic non-infectious diseases occurring in children [1, 2]. There appears to be a worldwide increase in type 1 diabetes in children and adolescents, the epidemiology of which remains largely unknown [3]. The incidence of type 1 diabetes is currently estimated at 5/100 000 new cases in the Western Cape compared to 2-35/100 000 new cases worldwide [4]. However, literature on diabetic complications and metabolic control in children and adolescents in the Western Cape is very limited. Literature regarding diabetes in Africa is also quite limited due to poor infrastructure and inadequate training of healthcare workers [5].

Once a patient is diagnosed with type 1 diabetes, it is important to obtain adequate metabolic control, so as to limit or delay the progression of complications as a result of the disease [6]. Metabolic control and early diagnosing of complications in type 1 diabetics could be improved by implementing a multi-disciplinary approach involving a diabetic specialist, diabetic educator, dietician and social worker as per the ISPAD (International Society for Pediatric and Adolescent Diabetes) clinical practice consensus guidelines [7, 8]. A study done by F.J. Cowan et al at the University Hospital of Wales also demonstrated a reduction in outpatient clinic non-attendance rate, length of hospital stay, median hospital stay at diagnosis and admission rates, a year after implementation of a DNE [9].

At TCH, a DMT (new paediatric endocrinologist, a dietician and social worker) was introduced in August 2007 whereas a dedicated DNE for paediatrics was only appointed in August 2009. These interventions are expected to improve metabolic control and clinic attendance as well as reduce hospital admissions, length of hospital stay and prevalence of complications, thus improving quality of life in these patients.

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## 2 LITERATURE REVIEW

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Glycosylated Haemoglobin (HbA1c) levels are used as the marker of long-term metabolic control, a predictor of the risk of development of complications in type 1 diabetics [10], and are a reliable method for diagnosing type 1 diabetes in both children and adolescents [11]. The American Diabetes Association, International Expert Committee and World Health Organisation currently recommend an HbA1c level of  $\geq 6.5\%$  to diagnose diabetes. However, the low sensitivity, higher cost and limited availability in developing countries compared to blood glucose levels currently make it an inappropriate diagnostic tool in these countries [12]. Good metabolic control is defined as an HbA1c level of  $< 7.5\%$  as per the ISPAD clinical practice consensus guidelines of the year 2000 and 2009 [6, 7, 10]. An HbA1c level of 7.5-9.0% and  $>9\%$  is considered as moderate and poor metabolic control, respectively [13]. However, many international studies [2], as well as African studies performed in Tanzania and Rwanda [5, 14], reveal that the recommended HbA1c level is seldom reached, due to numerous factors including patient-related and/or treatment-related factors [2, 5, 14]. Influencing factors in international studies include patient age, gender, ethnicity and socioeconomic status; follow-up centres and number of diabetic clinic visits. Increased HbA1c levels were associated with pubertal age as well as adolescents, female gender, ethnic minority status, poor socioeconomic status and fewer diabetic clinic visits [2]. African studies suggest that worse glycaemic control is associated with fewer clinic visits, longer diabetes duration and male gender as well as unstandardized management approaches. Lack of infrastructure resulting in poorly stored insulin as well as lack of adequate supply of glucose testing materials could also play a role in poorer glycaemic control [5]. A study by E.-M. Gerstl et al in 2008 in Germany and Austria suggests that HbA1c levels  $> 7.5\%$  are especially associated with an increased risk of development of microvascular complications [2].

Complications of type 1 diabetes mellitus could be categorised as microvascular or macrovascular [8]. Microvascular complications include diabetic retinopathy, nephropathy and neuropathy [15] whereas macrovascular complications include myocardial infarction and

cerebrovascular accident. Other associations include hypertension, hypercholesterolaemia, limited joint mobility, poor growth and high body mass index (BMI), the latter two factors being found more commonly in pubertal females.

Numerous studies including the Diabetes Control and Complications Trial (DCCT) have obtained data which suggests that improved glycaemic control as reflected by lower HbA1c levels, results in a reduced incidence of microvascular complications [2, 6, 8, 16] as well as a reduction in the progression of these complications. In the DCCT, every 10% reduction in the HbA1c reduced the risk of retinopathy progression by approximately 44%, microalbuminuria by 25% and clinical neuropathy by 30% in patients older than 13 years of age [16].

Diabetic retinopathy appears to be the most prevalent microvascular complication occurring in children and adolescents with type 1 diabetes. The prevalence appears to increase dramatically between five and fifteen years of diabetes and reaches a plateau in 80%-100% of patients after twenty years diabetes duration [17]. Diabetic retinopathy can be divided into an early non-proliferative (background) stage and a later proliferative stage [18]. However, studies demonstrating the prevalence of each individual category are very rare, even more so in children and adolescents.

In 1998, a study by R.W. Holl et al, demonstrated the prevalence of mild non-proliferative retinopathy in paediatric type 1 diabetics to be 16.3% of which 54% were males and 46% females. It was also found that both prepubertal and pubertal duration of diabetes appear to be relevant for the development of background retinopathy. However, with prepubertal onset of diabetes, the duration of time to the development of retinopathy is significantly shorter than with pubertal onset of diabetes [17]. In patients with an HbA1c level <7.5%, the median diabetes duration until retinopathy developed was 18.3 years compared to 15.5 years in patients with an HbA1c level >7.5% (defined as poor glycaemic control), thus demonstrating that poorer glycaemic control is associated with earlier onset of retinopathy [17]. A review by E.M. Kohner also suggests that improved glycaemic control can delay the onset and reduce the severity of diabetic retinopathy [19]. Good glycaemic control should therefore be the principal focus in all paediatric and adolescent patients irrespective of patient age or age of onset of diabetes [17].

Diabetic nephropathy is also a microvascular complication of concern. Paediatric and adolescent type 1 Diabetics have an increased risk of diabetic nephropathy which can eventually lead to renal failure. This can progress to end-stage renal failure which would eventually require dialysis and transplantation [20]. Microalbuminuria has been used worldwide as a preceding marker for the development of overt diabetic nephropathy [20, 21]. It is defined as a urine albumin to creatinine ratio (UAC)  $\geq 2\text{mg/mmol}$  in at least two of three consecutive early morning urine samples [21].

In the MIDAC (Microalbuminuria in Diabetic Adolescents and Children) study of 2000, it was found that 9.7% of patients between 10 and 20 years of age had microalbuminuria, placing them at risk of later developing diabetic nephropathy [21]. A study by Kiemans Raile et al (2007), which included children, adolescents and adults and was within 40 years of diabetes duration, demonstrated the prevalence of diabetic nephropathy to be 25.4% for persistent microalbuminuria but only  $<10\%$  for macroalbuminuria (UAC ratio  $\geq 35\text{mg/mmol}$ ) or end-stage renal disease. However, this study defined microalbuminuria with a UAC ratio  $\geq 2.5\text{mg/mmol}$  as per the American Diabetes Association guidelines [20]. The prevalence rate was found to be lower than that of various other studies done in Denmark, England and Western Australia with the most prominent difference being improved glycaemic control as demonstrated by lower HbA1c levels [20]. Overall, the prevalence of microalbuminuria in childhood increases with the age of the population under study ( $p < 0.001$ ) with risk factors including poor long-term (diabetes duration  $> 1$  year) glycaemic control, longer duration of diabetes and possibly hypertension [21, 22]. The mean HbA1c level was also found to be higher in patients with microalbuminuria than those with normal urinary albumin excretion ( $p = 0.001$ ). This strengthens the fact that improved glycaemic control would delay the development of diabetes-associated complications [21] and more specifically, microalbuminuria [22, 23].

A cohort study done by F. Mohsin et al (2005) and a study by E. Downie et al (2011), both in Australia, looked at trends in microvascular complications in adolescents with type 1 diabetes [15, 23]. With Mohsin's study, three time periods were analysed. It was found that retinopathy, early elevation of albumin excretion rate and microalbuminuria, declined significantly over time. The prevalence of retinopathy declined from 49% to 24% ( $p < 0.0001$ ), early elevation of albumin excretion rate declined from 38% to 25% ( $p = 0.022$ ) and microalbuminuria declined from 7% to 3% ( $p = 0.017$ ). However, the



prevalence of peripheral nerve abnormalities, as measured by quantitative sensory tests (i.e. vibration and thermal threshold) increased from 12% to 24% ( $p=0.0017$ ) [15]. With E. Downie's study, 4 time periods were analysed. There was also a reduction in the prevalence of retinopathy over time from 53% to 12% ( $p<0.001$ ) as well as microalbuminuria from 8% to 3% ( $p=0.006$ ), whereas borderline elevation of albumin excretion rate declined initially from 45% to 26% before reaching a plateau of 30% ( $p<0.001$ ). The prevalence of peripheral neuropathy increased from 7% to 14% ( $p=0.016$ ) [23].

A Rwandan study by S.L. Marshall et al (2013) demonstrated the rates of microalbuminuria, nephropathy and neuropathy to be 20.8%, 4.7% and 2.1% respectively with HbA1c being positive predictors for microalbuminuria. Clinical data and complication assessment was however incomplete and retinopathy was not investigated due to lack of diagnostic equipment [14]. A later study performed by S.L. Marshall et al in Rwanda in 2014 demonstrated the incidence of microalbuminuria and nephropathy to be 16.6% and 3.3% respectively however with the same concerns regarding incomplete data [24].

Dyslipidaemia is also associated with the development of diabetic nephropathy in children and adults with type 1 diabetes [20, 25] as well as with the development of macrovascular (cardiovascular) disease in high risk diabetics [26]. Raised LDL cholesterol and triglycerides appear to be independently associated with microalbuminuria [20]. A substantial proportion of young diabetic patients have abnormal serum lipids with prevalence in type 2 diabetics being higher than in type 1 diabetics > 10 years of age. This SEARCH for Diabetes in Youth Study demonstrates that 20% of type 1 diabetics  $\geq 10$  years of age have Total Serum Cholesterol (TSC) concentrations  $>5.7\text{mmol/l}$  [27]. Abnormal serum lipids were found in 73.5% of type 1 diabetic children in a study by I. Sylvester at the Muhimbili National Hospital in Dar es Salaam in 2012, with a raised LDL cholesterol of 29.6%, high TSC of 25.5%, low LDL cholesterol of 13.3% and high triglycerides of 5.1%. Abnormal lipid profile was associated with worsening glycaemic control but this was not confirmed with statistical tests [26].

Limited joint mobility (LJM), also known as juvenile diabetic cheiroarthropathy, although not classified as a complication of diabetes, has been reported in many studies, occurring in type 1 diabetics [28, 29, 30, 31, 32]. LJM is described as a non-painful contracture of finger joints [29]. Prevalence varies

between studies from 26% to 65.1% and is dependent on the method used to evaluate this clinical feature [28, 29, 30, 31, 32], longer duration of diabetes [28, 29, 31, 32] and presence of microalbuminuria [29, 32] and retinopathy [29, 30, 32]. Qualitative methods involve assessment using the prayer manoeuvre [28, 29, 30, 31, 32], whereas quantitative methods measures the angles of maximal flexion and extension of the fifth and third metacarpophalangeal joints and wrist [28, 29].

In order to limit these complications and maintain adequate metabolic control in the type 1 diabetics, insulin therapy remains the mainstay of treatment. The basal bolus regimen (multiple injections/day) is now being considered to be the gold standard by most paediatric diabetologists [33]. This regimen aims to mimic the physiological insulin profile as seen in non-diabetics as well as to allow flexibility required by the lifestyle needs of diabetic children and is therefore the better treatment option compared to conventional insulin therapy (one or two injections/day) which is a compromise between convenience and the potential for achieving target plasma glucose levels.

Metabolic control and early diagnosing of complications in type 1 diabetics could also be improved by implementing a multi-disciplinary approach involving a diabetic specialist, diabetic educator, dietician and social worker as per the ISPAD clinical practice consensus guidelines [7, 8].

A study by M. O'Hagan and J.N. Harvey investigated specifically, the influence of a DNE on glycaemic control over a period of 6 years. They found improved glycaemic control in centres where a DNE had been appointed from an HbA1c of  $9.59 \pm 1.88\%$  (mean  $\pm$  SD) to  $8.72 \pm 1.61\%$  (mean  $\pm$  SD) ( $p < 0.001$ ). This improvement was not attributed to increased prescribed insulin dose as increased insulin dose was associated with poorer glycaemic control. DNEs were found to have a supportive and educational role with increased contact with patients and their families resulting in the greatest improvement in glycaemic control of children  $>10$  years of age ( $p = 0.047$ ). This suggests that DNEs may have a positive influence on behavioural factors present in adolescence [34].

Statistically significant improved metabolic control ( $p < 0.001$ ) from  $8.7 \pm 1.8\%$  (mean  $\pm$  SD) to  $8.1 \pm 1.5\%$  (mean  $\pm$  SD), with a reduction in HbA1c of 0.038%

per year (95%CI 0.032-0.043%) was also documented in a study by J. Rosenbauer et al. This also suggests the improvement is as a result of the implementation of a multi-disciplinary diabetes team as well as increasing patient education [13].

A study done by F.J. Cowan et al at the University Hospital of Wales investigated outpatient clinic non-attendance rate, median hospital stay at diagnosis and admission rates, a year after implementation of a DNE. Clinic non-attendance decreased significantly from a median of 19% to 10% ( $p<0.001$ ) in the paediatric clinic and from 38% to 23% ( $p<0.05$ ) in the adolescent clinic, median hospital stay at diagnosis dropped from 5 days to 1 day ( $p<0.001$ ) and admission rates at diagnosis was reduced from 100% to 41.7% [9].

In a recent Tanzanian study by L.J. Mukama et al at the Kilimanjaro Christian Medical Centre (2013), HbA1c levels did not improve 6 months after the implementation of a diabetes management program, despite regular clinic attendance, diabetes education and insulin provision. Factors associated with worse glycaemic control included fewer clinic attendances, longer diabetes duration, larger insulin doses and male gender. Despite HbA1c levels not reaching statistical significance, there was a downward trend from 12.4% to 11.2%. It is most likely that a longer period of study is needed to observe a statistically significant improvement in glycaemic control [5].

A DMT was introduced at TCH in August 2007. The team consisted of a newly appointed paediatric endocrinologist, a dietician, a social worker and the ward nursing staff. A dedicated DNE for paediatrics was only appointed by the university to work at TCH in August 2009, because the hospital management did not consider her post a priority at the time. This appointment was expected to improve metabolic control, education of patients and caregivers, clinic attendance and reduce hospital admissions as deduced from other studies [9, 34].

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### **3 AIMS**

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To determine the effectiveness of the diabetes management team and a DNE in improving glycaemic control and other outcome measures of paediatric diabetes care.

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## 4 OBJECTIVES

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To perform a study of the type 1 diabetic paediatric and adolescent patients attending the diabetic clinic at Tygerberg Children's Hospital over 4 time periods: August 2004-July 2005 (Period 1); August 2007-July 2008 (Period 2); August 2009-July 2010 (Period 3); and September 2010-July 2011 (Period 4) to determine:

- 1 glycaemic control;
- 2 the admission rate for diabetic ketoacidosis (DKA), recurrent DKA and uncontrolled diabetes;
- 3 length of hospital stay;
- 4 clinic attendance rate;
- 5 insulin dose/kg;
- 6 % of patients on the intensive insulin regimen; and
- 7 the prevalence of microvascular complications (nephropathy, retinopathy and neuropathy), limited joint mobility and dyslipidaemia.

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## 5 HYPOTHESIS

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It was hypothesised that the introduction of a full DMT (which includes a DNE) for the care of children and adolescents with T1DM at TCH would 1) improve the glycaemic control (as measured by the HbA1c), 2) decrease the DKA and rDKA rates, 3) reduce admission rates, 4) shorten the length of hospital stay, 5) improve clinic attendance rate, 6) lead to a reduced dose of insulin per patient, 7) facilitate the use of an intensive insulin regimen, and 8) decrease the prevalence of complications.

## 6 METHODOLOGY

### 6.1 STUDY DESIGN

This is a retrospective cohort study (a time series) with cross-sectional elements.

### 6.2 DEFINITIONS

<b>Adolescent:</b>	Patients 13-17 years 11 months of age.
<b>Glycaemic control is indicated by the:</b>	
• <b>HbA1c level:</b>	<p>&lt;7.5%: good control</p> <p>7.5-8.4%: acceptable control</p> <p>&gt;8.5%: poor control</p> <p>&gt;14%: very poor control [8, 13]</p>
<b>Limited joint mobility (LJM):</b>	A complication of type 1 diabetes mellitus, which is a cutaneous condition characterised by thickened skin of the hands and fingers, leading to flexion contractures which impairs joint mobility [35].
<b>Microalbuminuria:</b>	Urine albumin to creatinine ratio (UAC) $\geq$ 2mg/mmol in at least two of three consecutive early morning urine samples [21].
<b>Recurrent DKA:</b>	$\geq$ 2 DKA episodes [36]

**Time periods:**

- **Period 1 (P1):** August 2004-July 2005
- **Period 2 (P2):** August 2007-July 2008
- **Period 3 (P3):** August 2009-July 2010
- **Period 4 (P4):** September 2010-July 2011

### **6.3 SUBJECTS**

T1DM children and adolescents attending the paediatric diabetes clinic at TCH.

### **6.4 PATIENT INCLUSION AND EXCLUSION CRITERIA**

Patients were included if:

- a) they required insulin therapy after the neonatal period but before adolescence, irrespective of whether T1DM was confirmed on low serum C-peptide levels and elevated anti-glutamic acid decarboxylase (GAD) /Islet Antigen 2 (IA2) antibodies or not;
- b) they were managed during the following time periods: August 2004-July 2005 (P1): before a diabetic management team was introduced, but a paediatric endocrinologist was on site; August 2007-July 2008 (P2): introduction of DMT after a period when no paediatric endocrinologist was available; August 2009-July 2010 (P3): introduction of a DNE; and September 2010-July 2011 (P4): after substitution of the DNE.

The following patients were excluded: known patients with type 2 diabetes, monogenic and secondary forms of diabetes.

### **6.5 ETHICAL APPROVAL**

Ethics approval was applied for and obtained from the Committee for Human Research at the University of Stellenbosch. As it was a retrospective folder review, a waiver of Informed Consent was obtained from the Medical Superintendent of TCH. Confidentiality was maintained by assigning a case number to each patient.



## 6.6 METHODS

The following data was captured: age, sex, age at diagnosis (in years and months), ethnicity, HbA1c (mean HbA1c's at the end of each time period of all the patients occurring in that time period), lipid profiles [total serum cholesterol (TSC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC) and triglycerides (TG)], UAC ratio (mean UAC's at the end of each time period of all the patients occurring in that time period), presence/absence of retinopathy, neuropathy and limited joint mobility, hospital admissions, reason for admission (i.e. diabetic ketoacidosis or uncontrolled diabetes), duration of hospital stay (in days), and number of clinic attendances/year. Data also included type of insulin (short/rapid or intermediate acting), number of insulin injections/day and insulin doses with a hospital/clinic visit (at the end of the time period).

Various data sources were used to collect the data: Computerised diabetic register of current patients established by the DNE; the buffers of old and current patients kept at the clinic, patient folders which were accessed through the hospital records using ICD 10 codes for all diabetics (Type 1, Type 2 and other) from 0-18 years of age, and laboratory data stored by the National Health Laboratory Service (NHLS).

The data was checked for missing and suspicious values. For patients where day of the month of diagnosis was unknown, the 15<sup>th</sup> of that month was used (36 patients). For patients where the month of the year of diagnosis was unknown, the 30<sup>th</sup> June was used (2 patients).

HbA1c EDTA specimens were initially analysed in the laboratory until 2009. The method used for measuring HbA1c was standardised according to the National Glucose Standardisation Program (NGSP) and is the same method used by the DCCT. From 2009, HbA1c capillary specimens were analysed using a point of care device, the Siemens DCA Vantage Analyzer. The 2 methods were compared by the NHLS in 35 subjects. The within assay coefficient of variation (CV) was 1.2% for the low control HbA1c of 5.1% and 4.3% for the high control HbA1c of 12.9%, whereas the between assay CV was 2.4% for the low control and 3.2% for the high control. Both assays were well within the acceptable CV of 5%. The precision quality requirements for

the analyzer were within the recommended targets of 14% and 18% (unpublished personal communication by Dr M.A. Rensburg, Chemical Pathologist, Tygerberg Hospital).

## 6.7 STATISTICAL ANALYSIS

The data was analysed by the Statistical Department of The University of Stellenbosch, using Statistica 11 (2013). Statistical analysis was performed on the total patient group as well as on the patient group who had data in all 4 time periods.

A 5% significance level was applied throughout. Friedman's ANOVA was used to compare changes in a specific variable over time (patient group who had data in all 4 time periods). Results were obtained for several combinations of the 4 different periods and in each case only those patients with available data at each of the periods in the respective combination for a particular variable were included. Box and whisker plots, representing the mean, standard error (SE) and 95% confidence intervals were used to describe the distribution of each parameter within a specific period. P-values were also generated for the numerical data.

With regards to the total patient group, box and whisker plots representing the mean, standard error (SE) and 95% confidence intervals were also used to describe the distribution of each parameter within a specific period. Median values were also generated for the numerical data.

Pearson's chi-squared test was used to compare differences between insulin categories and a combination of gender and age categories.

Generalised Estimating Equations (GEE) were used to determine whether there was a significant change over the periods in LJM.

## 6.8 LIMITATIONS

Some of the limitations are those typical of a retrospective study i.e. 1) inadequate documentation of clinical and biochemical data by the attending

medical doctors, 2) lost or misplaced clinical records, and 3) microfilmed data in the older diabetic patients that were of poor quality. The remaining limitations are unique to this particular study.

All patients did not have confirmatory testing of their UAC ratio as per the recommended guidelines and transient microalbuminuria could not be distinguished from persistent microalbuminuria. Also, limited joint mobility was not assessed during Period 1.

Insulin resistance which is associated with obesity or an increasing weight could lead to Type 2 diabetes. Insulin insufficiency results in Type 1 diabetes. If a T1DM child is obese, insulin resistance to the administered insulin may also occur [37]. Data regarding BMI was however not collected. This would have been problematic if the patients' BMI increased over time, because of a high BMI being associated with insulin resistance. As a result, the HbA1c would have been expected to rise. The opposite was actually the case – the HbA1c decreased over time. One can therefore only assume that weight increase was not a significant confounder with regards to the results obtained.

When analysing HbA1c levels, patients in various stages of diabetes were included in period 1, resulting in a heterogeneous group of patients. Depending on the criteria used, 2-8 patients were probably in the honeymoon phase (although none of these had an HbA1c < 7%). This could have artificially reduced the mean HbA1c in period 1, making a direct comparison of the various periods more difficult.

Puberty data was not captured when analysing HbA1c levels. However, using age criteria to define puberty (boys  $\geq 12$  years and girls  $\geq 11$  years of age), it was found that 18 of 22 patients were in puberty in period 4 also resulting in a heterogeneous group of patients. The expected result would be an inflated HbA1c, with poorer control and more complications due to associated insulin resistance, as well as insulin omission during this rebellious phase of life.

Children grow and develop over time. At 18 years of life, patients were being referred to the adult service for further management. Similarly, new patients were being diagnosed during all periods. The patient population was therefore

not static. Hence, most analysis had to be limited to those patients observed during all 4 time periods. As a consequence, sample size was reduced and variable for the different parameters that were assessed. Irrespective of this, statistically significant changes could still be identified.

Ideally, a longer duration of study is needed after employment of any DNE, as considerable time is needed for training and gaining experience. Furthermore, any educational intervention in any particular chronic disease will take considerable time to be effective. This is particularly true for admission rates and HbA1c levels. Unfortunately, due to unforeseen circumstances, a second DNE had to be employed during the study period. Under ideal conditions, the effect of a single DNE should have been assessed after 2 years, as one cannot assume that the 2 DNEs would perform exactly the same.

About 25% of patients reside in rural areas. Because of the long distances to the academic hospitals, patients from these areas presenting in DKA may have preferentially been treated at a district hospital without being transferred to the tertiary centre. Teenagers in DKA on the other hand may present to the adult emergency unit and be managed further in the adult diabetes service. The DKA and rDKA rates may therefore actually be higher than documented in this study. Bias towards any particular time period is not to be expected, because the number of patients in DKA, not presenting to the Paediatric Endocrine Unit, can be expected to be fairly constant during any given period.

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## 7 RESULTS

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A total of 190 paediatric and adolescent patients with type 1 diabetes were included over the 4 time periods. However, within the various time periods, new patients were diagnosed, patients were lost to follow-up and some patients were transferred to the adult diabetic clinic. Also, many patients were seen in some time periods, but not in others. These factors therefore resulted in varying patient numbers per time period but with a cumulative increase in the number of patients as time progressed. Period 1 comprised a total of 77 patients on treatment. At this stage 113 patients were yet undiagnosed, adding up to the total of 190. Period 2 comprised of 112 patients on treatment, 57 undiagnosed patients, 8 patient transfers and 13 patients lost to follow-up (190 patients). Period 3 comprised of 135 patients, 19 undiagnosed patients, 9 patient transfers and 27 patients lost to follow-up (190 patients). Period 4 comprised of 139 patients, 16 adult clinic transfers and 35 patients who were lost to follow-up (190 patients). Also, due to missing data, the number of values/measurements is not consistent across all variables.

### 7.1 PATIENT CHARACTERISTICS

The patient characteristics are shown in table 1.

There was a female predominance of 65.3% compared to males. The highest proportion of patients with type 1 diabetes was seen in the age category of pre-pubertal girls (46.3%).

With regards to the types of insulin therapy, the Human soluble insulin and NPH insulin combination were more commonly used than the insulin analogues as these are more freely available in the public sector.

The following was missing for one patient: age at diagnosis, age category based on sex and types of insulin therapy.

**Table 1: Patient characteristics (all patients)**

Characteristic		n (%)
<b>Age at diagnosis (years)<sup>1</sup></b>	<2	15 (8)
	2-10	88 (46.3)
	≥ 10	86 (45)
<b>Age category based on gender (years)<sup>2</sup></b>	Boys<12	49 (25.8)
	Boys ≥12	17 (8.9)
	Girls<11	88 (46.3)
	Girls≥11	35 (18.4)
<b>Sex</b>	Male	66 (34.7)
	Female	124 (65.3)
<b>Ethnicity</b>	Coloured	143 (75.3)
	Black	25 (13.2)
	White	22 (11.6)
<b>Types of Insulin therapy<sup>3</sup>: Short-acting</b>	Human Soluble Insulin	164 (86.8)
	Rapid Acting Insulin Analogue	25 (13.2)
<b>Intermediate-acting</b>	NPH Insulin	181 (95.3)
	Long Acting Insulin Analogue	9 (4.7)

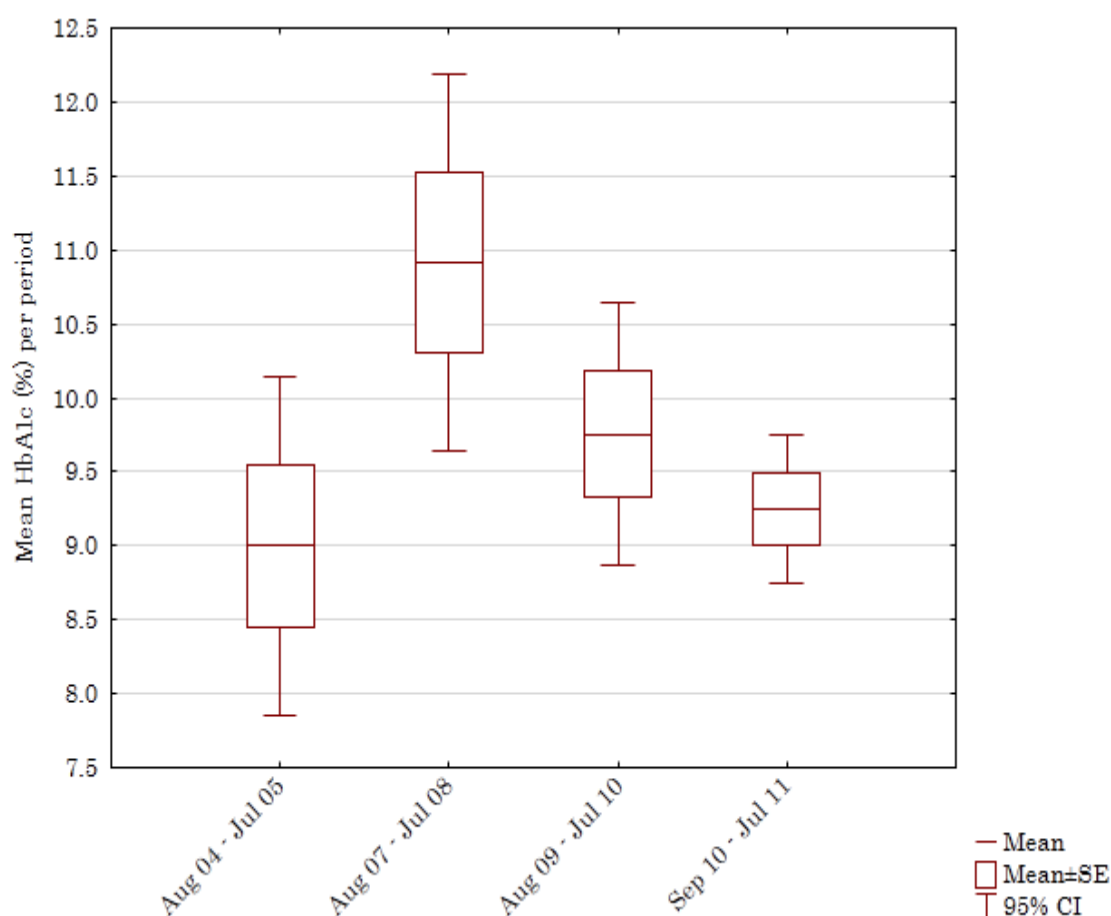
<sup>1</sup> Age data missing in 1 patient

<sup>2</sup> Age category based on sex data missing in 1 patient

<sup>3</sup> Types of insulin therapy data missing in 1 patient

## 7.2 GLYCAEMIC CONTROL

Twenty two patients had HbA1c data in all 4 time periods (figure 1). The mean HbA1c increased from 9% (95% CI 7.85-10.15) in period 1 to 10.9% (95% CI 9.6-12.2) in period 2, and decreased to 9.25% (95% CI 8.75-9.75) in period 4 ( $p=0.01818$ ).



**Figure 1: HbA1c levels per time period (for patients with HbA1c in all 4 time periods)**

Table 2 shows the characteristics of the patients with HbA1c levels captured in all 4 time periods. The age at diagnosis, age category based on gender, ethnicity and types of insulin therapy compares well with the total patient group. With regards to gender, there is an equal distribution of males and females compared to a female predominance in the total patient group.

**Table 2: Patient characteristics of patients with HbA1c levels captured in all 4 time periods**

Characteristic		n (%)
<b>Age at diagnosis (years)</b>	<2	3 (13.64)
	2-10	14 (63.6)
	≥ 10	5 (22.73)
<b>Age category based on gender (years)</b>	Boys<12	11 (50)
	Boys ≥12	0
	Girls<11	11 (50)
	Girls≥11	0
<b>Sex</b>	Male	11 (50)
	Female	11 (50)
<b>Ethnicity</b>	Coloured	18 (81.82)
	Black	2 (9.09)
	White	2 (9.09)
<b>Types of Insulin therapy: Short-acting</b>	Human Soluble Insulin	21 (95.45)
	Rapid Acting Insulin Analogue	1 (4.55)
<b>Intermediate-acting</b>	NPH Insulin	21 (95.45)
	Long Acting Insulin Analogue	1 (4.55)

As can be seen from table 3, the proportion of patients with good and acceptable glycaemic control initially decreased, but then increased again in period 4. The percentage of patients with very poor control doubled from period 1 to period 2, but declined again in periods 3 and 4 to less than half of the original proportion. Period 1 comprised a total of 64 patients with data and 13 patients with missing data (77 patients). Period 2 comprised a total of 93 patients with data and 19 patients with missing data (112 patients). Period 3 comprised a total of 101 patients with data and 34 patients with missing data (135 patients). Lastly period 4 comprised a total of 122 patients with data and 17 patients with missing data (139 patients).



**Table 3: Level of glycaemic control per time period (all patients)**

		Aug 2004- July 2005	Aug 2007- July 2008	Aug 2009- July 2010	Sept 2010- July 2011
		n (%)	n (%)	n (%)	n (%)
HbA1c <sup>4</sup>	Good control <sup>5</sup>	12 (18.8)	7 (7.5)	4 (4)	13 (10.7)
	Acceptable control <sup>6</sup>	12 (18.8)	3 (3.2)	11 (10.9)	16 (13.1)
	Poor control <sup>7</sup>	35 (54.7)	69 (74.2)	83 (82.2)	89 (73)
	Very poor control <sup>8</sup>	5 (7.8)	14 (15)	3 (3)	4 (3.3)

<sup>4</sup> Patients with missing data not included

<sup>5</sup> Good control: <7.5%

<sup>6</sup> Acceptable control: 7.5-8.4%

<sup>7</sup> Poor control: >8.5%

<sup>8</sup> Very poor control: >14% [8, 13]

### 7.3 DKA

The DKA rate showed improvement as time progressed, whereas the rDKA rate dropped drastically from period 1 to period 2 and thereafter remained static (table 4 and 5). In all time periods more girls presented with rDKA than boys.

**Table 4: Prevalence of DKA per time period (all patients)**

	<b>DKA rate (per 100 patient years)</b>
<b>Aug 2004-July 2005</b>	32.5
<b>Aug 2007-July 2008</b>	27.7
<b>Aug 2009-July 2010</b>	26
<b>Sept 2010-July 2011</b>	23.5

**Table 5: Prevalence of rDKA<sup>9</sup> per time period (all patients)**

	<b>Total</b>	<b>Males</b>	<b>Females</b>
	<b>n (%)</b>	<b>n (%)<sup>2</sup></b>	<b>n (%)</b>
<b>Aug 2004-July 2005</b>	6 (18.8)	2 (33.3)	4 (66.7)
<b>Aug 2007-July 2008</b>	5 (10)	2 (40)	3 (60)
<b>Aug 2009-July 2010</b>	6 (10.3)	1 (16.7)	5 (83.3)
<b>Sept 2010-July 2011</b>	5 (9.6)	2 (40)	3 (60)

<sup>9</sup> Recurrent DKA:  $\geq 2$  DKA episodes [36]

## 7.4 NUMBER OF ADMISSIONS, LENGTH OF HOSPITAL STAY AND NUMBER OF CLINIC ATTENDANCES

**Table 6: Number of admissions, length of hospital stay and number of clinic attendances of paediatric diabetes patients per time period (all patients)**

		Aug 2004- July 2005	Aug 2007- July 2008	Aug 2009- July 2010	Sept 2010- July 2011
		n (%)	n (%)	n (%)	n (%)
Number of admissions <sup>10</sup>	0	31(49.2)	50(50)	70(54.7)	85(61.6)
	1	21(33.3)	32(32)	48(37.5)	42(30.4)
	2	9(14.3)	16(16)	8(6.3)	8(5.8)
	>2	2(3.2)	2(2)	2(1.6)	3(2.2)
Length of stay (days) <sup>11</sup>	≤ 7	10(33.3)	6(12)	11(19)	10(18.9)
	7-14	8(26.7)	14(28)	14(24.1)	18(34)
	14-30	12(40)	15(30)	23(39.7)	17(32)
	>30	0	15(30)	10(17.2)	8(15.1)
Number of clinic attendances <sup>12</sup>	≥4	48(67.6)	55(51.9)	88(67.2)	77(55.8)
	<4	23(32.4)	51(48.1)	43(32.8)	61(44.2)

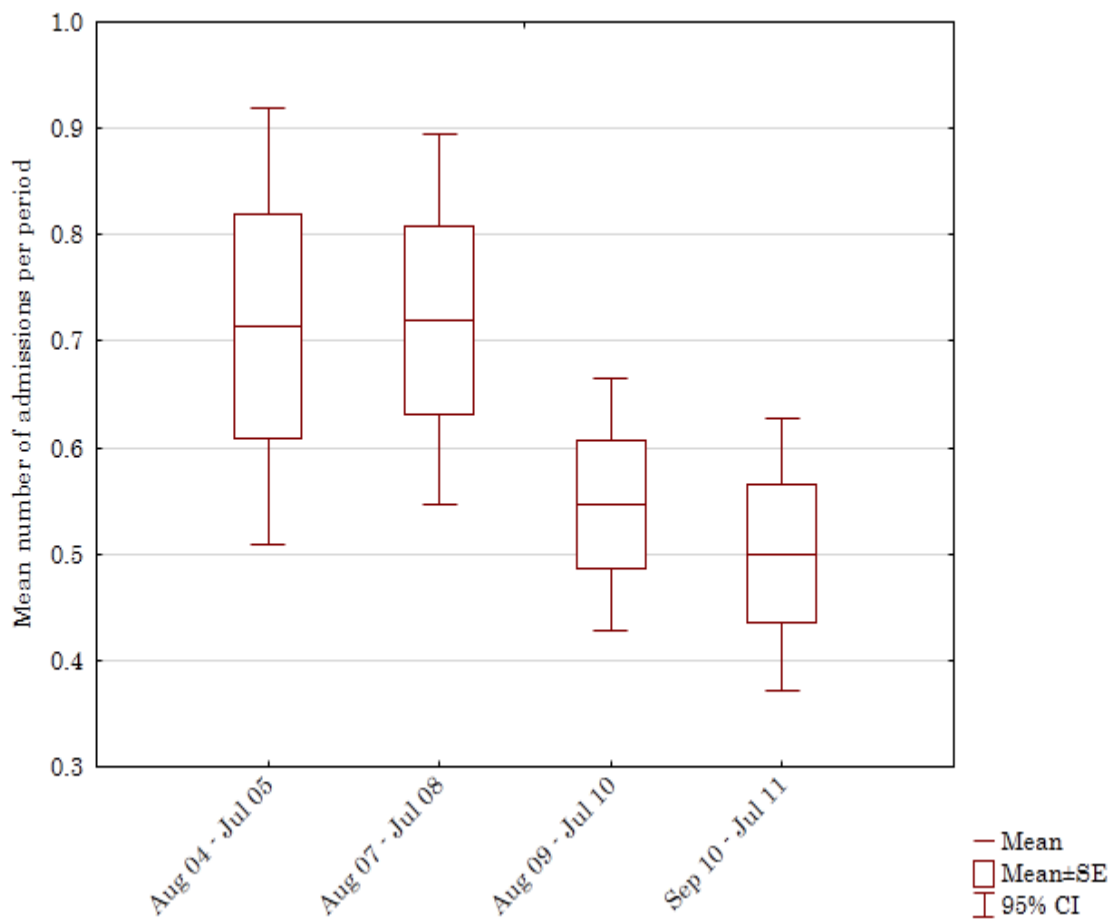
<sup>10</sup> Patients with missing data not included

<sup>11</sup> Patients with missing data not included

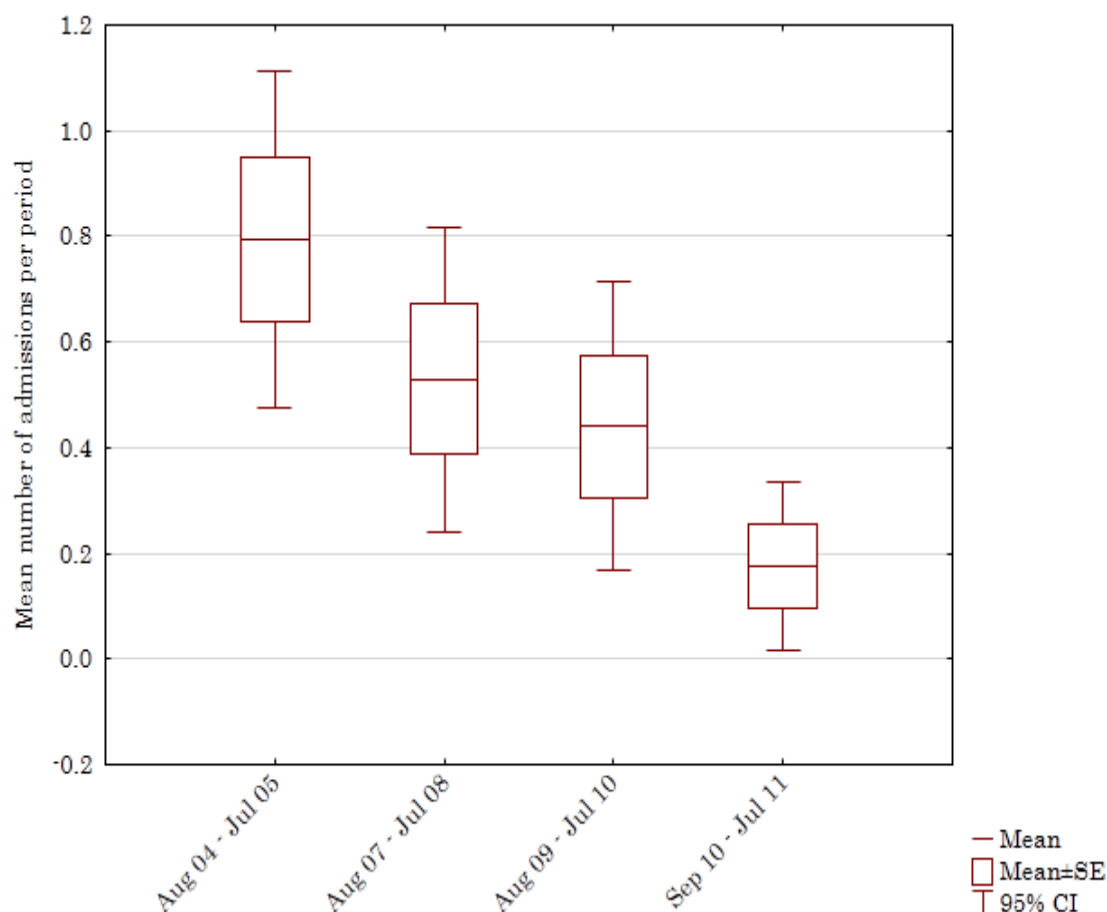
<sup>12</sup> Patients with missing data not included

### **Number of admissions**

The total numbers of patients with  $\geq 1$  hospital admission were 32/77 (the denominator indicates the total no of patients in the period) for period 1, 50/112 for period 2, 58/135 for period 3, and 53/139 for period 4. There were missing data for 14 patients in period 1, 12 patients in period 2, 7 patients in period 3 and 1 patient in period 4. The number of all admissions (for both DKA and poor glycaemic control) decreased during time periods 3 and 4 (figure 2). The proportion of patients who had no admissions increased progressively from 49.2% in period 1 to 61.6 % in period 4, while the proportion with 2 admissions decreased from 14.3% in period 1 to 5.8 % in period 4 (table 6). For patients captured in all 4 time periods, the number of admissions decreased with each time period (figure 3). This was found to be highly statistically significant ( $p=0.0127$ ).



**Figure 2: Number of admissions per time period (all patients)**



**Figure 3: Number of admissions per time period (patients captured in all 4 time periods)**

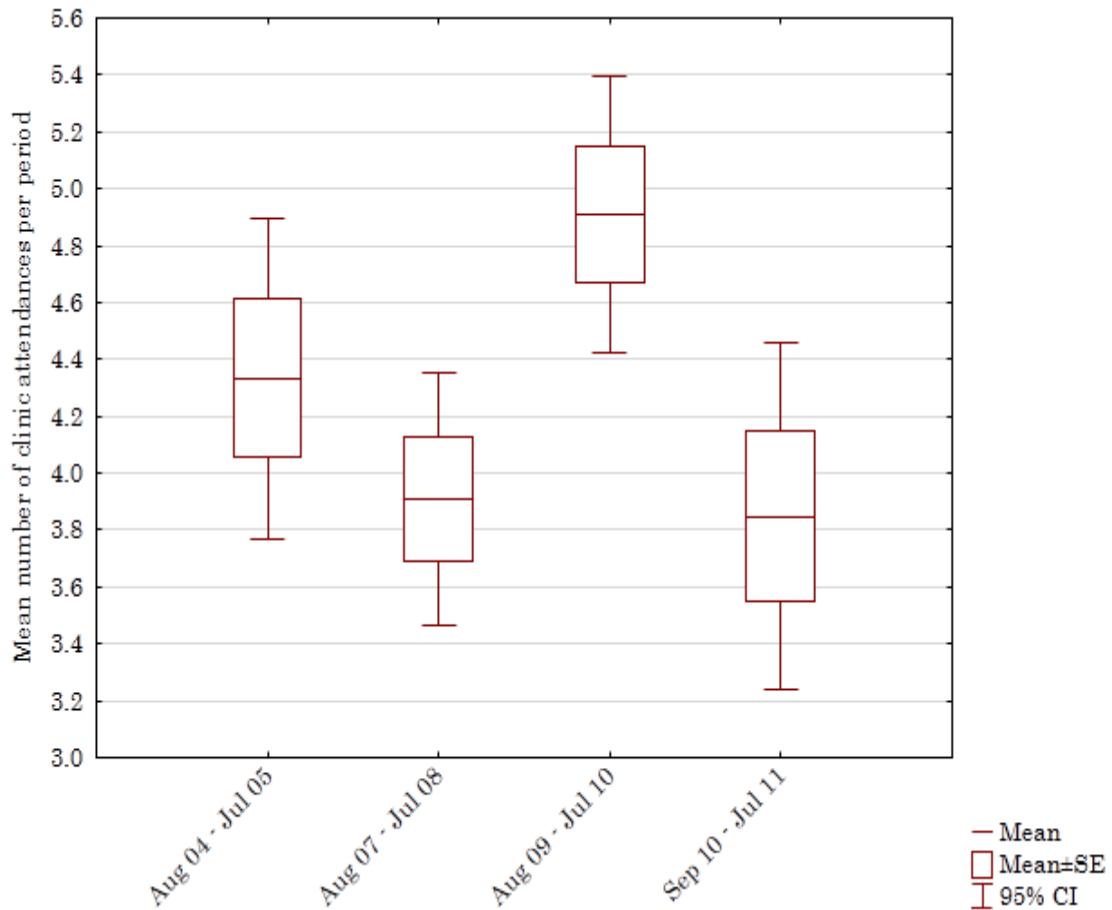
### **Length of hospital stay**

As can be seen from table 6, period 1 is characterised by shorter hospital stays. From period 2 hospital stays are longer. The proportion of patients staying longer than 30 days subsequently decreased again from 30% in period 2 to 15.1 % in period 4. For those patients documented to have  $\geq 1$  number of admissions, there was missing data for only 2 patients in period 1.

### **Number of clinic attendances**

As can be seen in figure 4, for patients captured in all 4 time periods, the mean number of clinic attendances were variable at 4.3 (95% CI 3.76-4.9) in period 1; 3.9 (95% CI 3.44-4.34) in period 2; 4.9 (95% CI 4.4-5.4) in period 3 and 3.8 (95%CI 3.24-4.44) in period 4 ( $p=0.00859$ ). A similar pattern was observed for all patients (table 6). There were missing data for 6/77 patients in

period 1, 6/112 patients in period 2, 4/135 patients in period 3 and 1/139 patients in period 4.



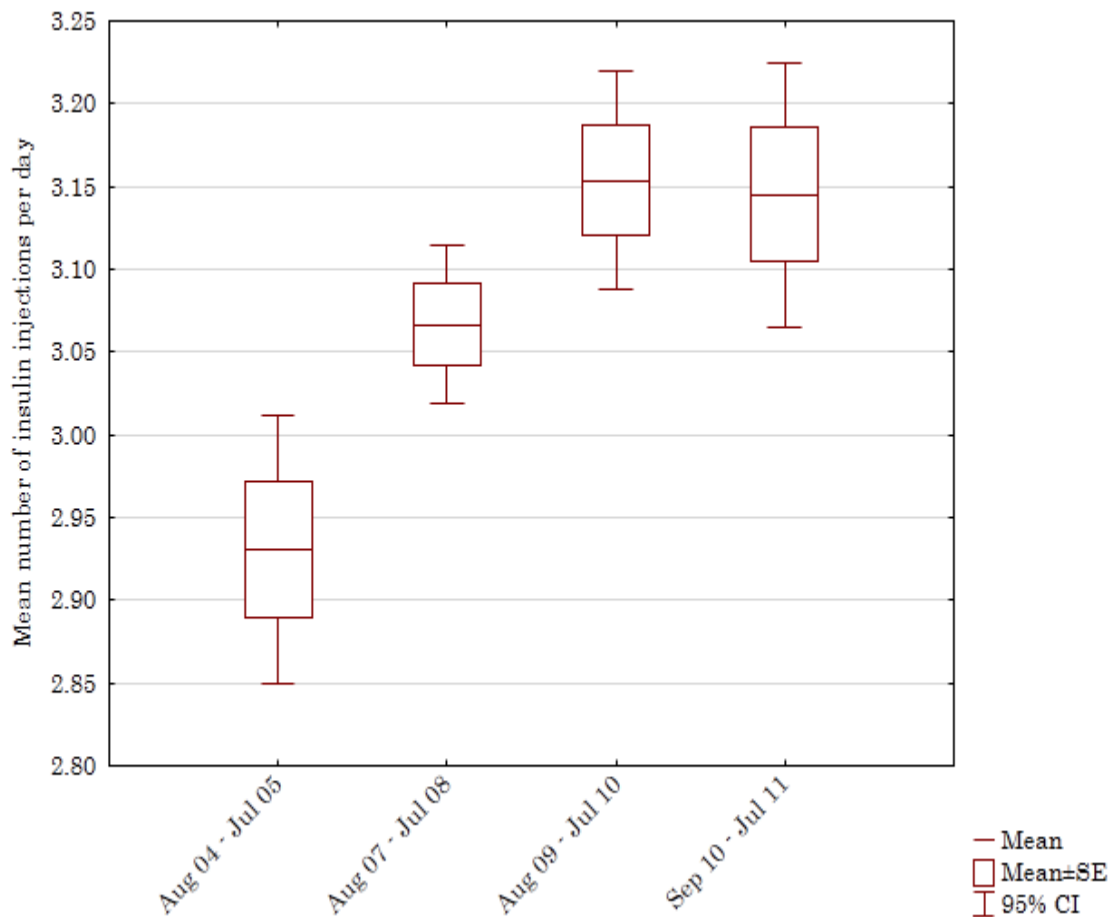
**Figure 4: Number of clinic attendances per time period (patients captured in all 4 time periods)**

## 7.5 INSULIN THERAPY

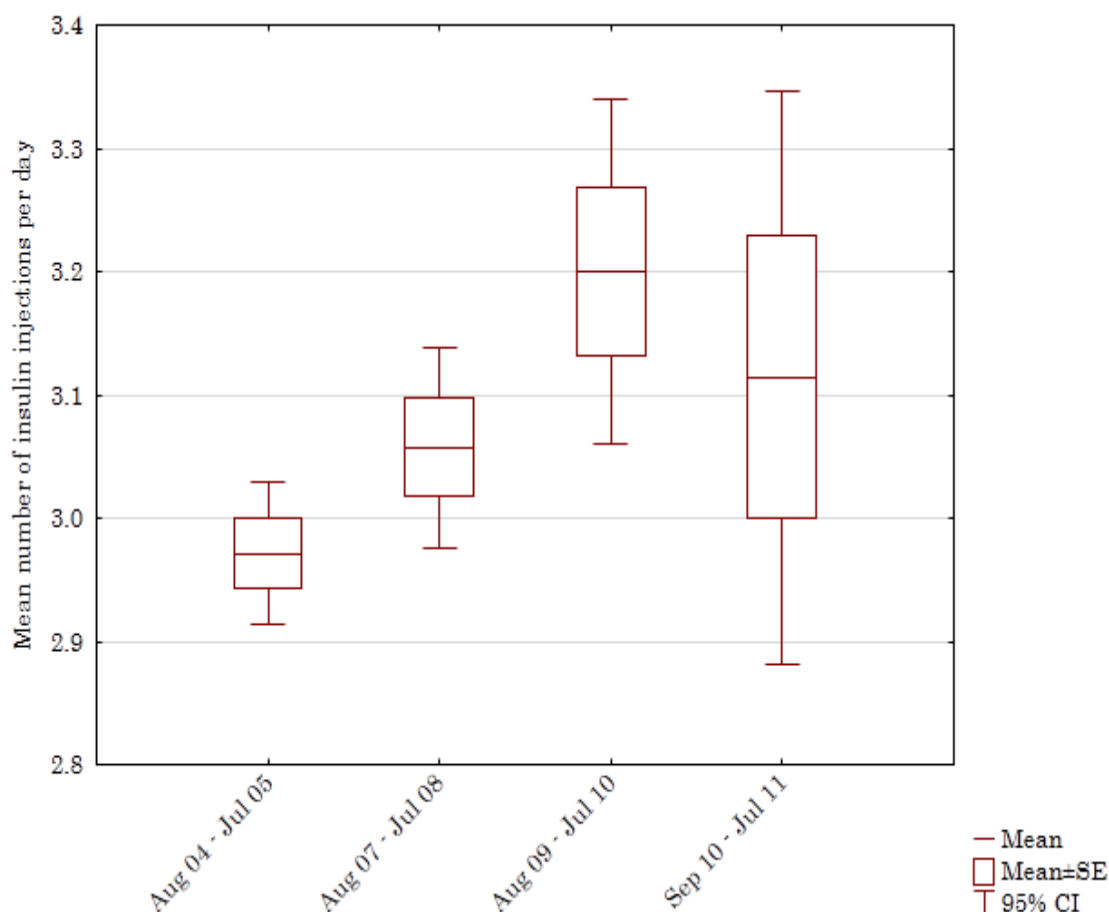
### Number of insulin injections per day

The number of insulin injections per day increased over time from 2.93 (95% CI 2.85-3.01) in period 1 to 3.14 (95% CI 3.06-3.23) in period 4 (figure 5). When comparing the 35 patients with data in all 4 time periods for number of insulin injection per day (figure 6), the mean number of insulin injections increased from 2.97 in period 1 to 3.11 in period 4 ( $p=0.0015$ ). For the total patient group (figure 5); during period 1, 7 patients (9.7%) were on 2 insulin injections/day, 63 patients (87.5%) were on the modified conventional

regimen of 3 insulin injections/day and 2 patients (2.8%) were on the basal bolus regimen of  $\geq 4$  insulin injections/day. During period 4, the number of patients on 2 insulin injections/day decreased to 1, 112 patients (81.8%) were on the modified conventional regimen and the number of patients on the basal bolus regimen increased to 24 patients (17.5%). 5 patients had missing data in period 1 and 2 patients had missing data in period 4.



**Figure 5: Number of insulin injections/day per time period (all patients)**

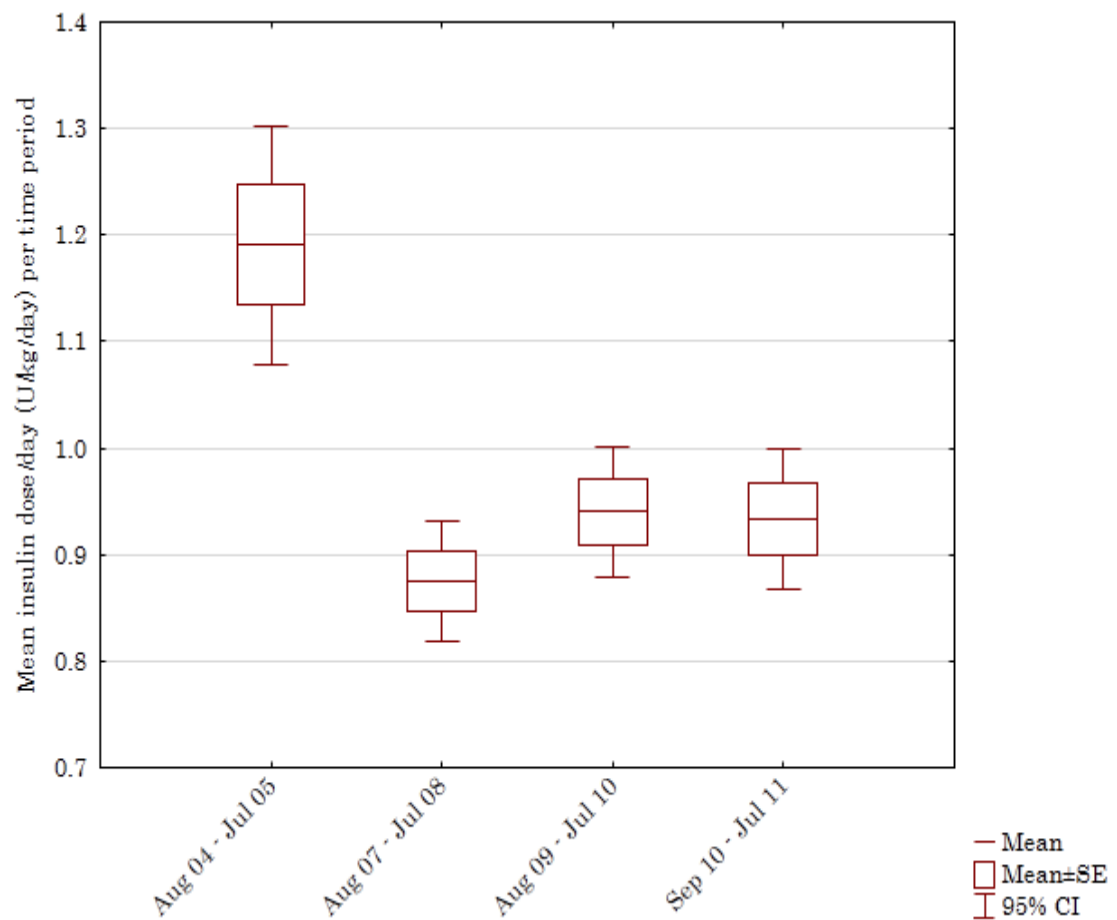


**Figure 6: Number of insulin injections/day per time period (patients captured in all 4 time periods)**

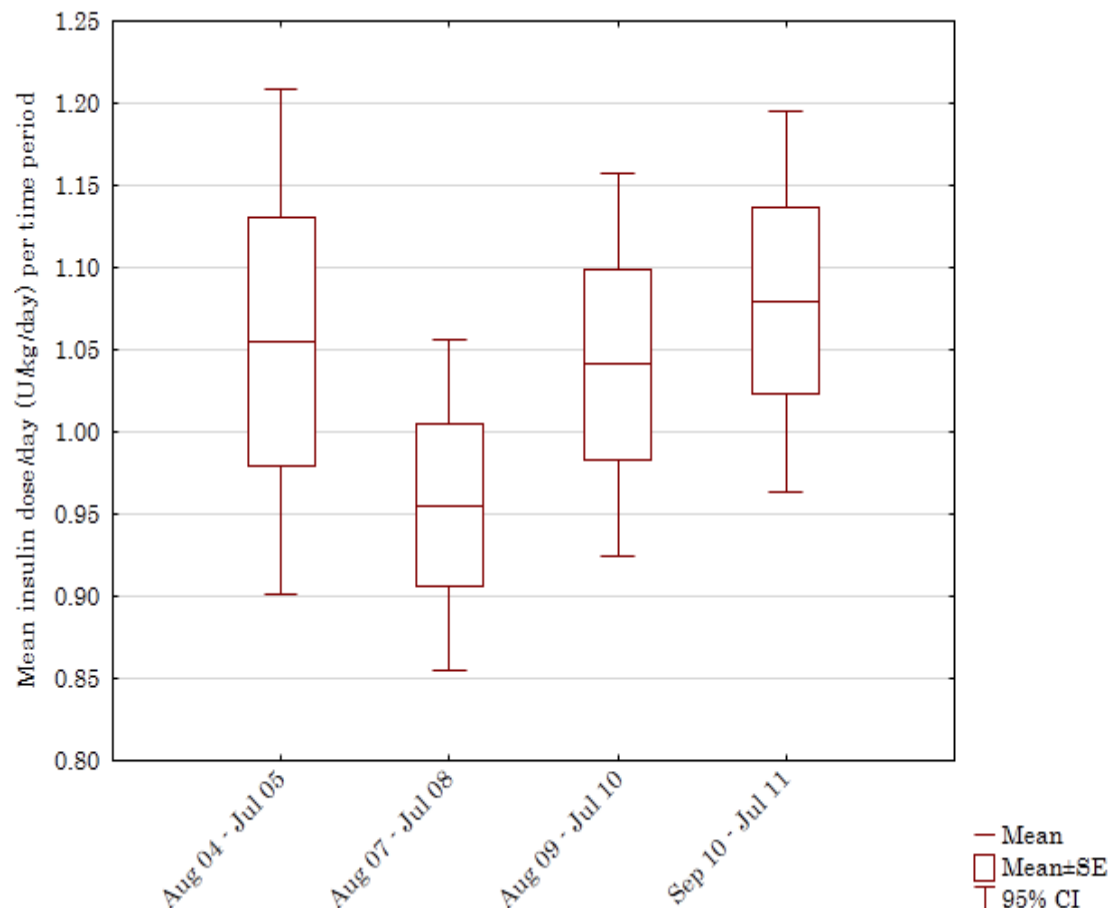
### **Insulin dose per day**

As can be seen in figure 7, the mean insulin dose for all patients in period 1 was significantly higher than in the other 2 groups i.e. 1.19 u/kg/day (95%CI 1.077-1.305) versus 0.88 u/kg/day (95%CI 0.818-0.933) in period 2, 0.94 (95% CI 0.878-1.003) in period 3 and 0.93 (95%CI 0.867-0.9984) in period 4. A similar trend was seen when analysing patients seen in all 4 time periods (figure 8), but significance was lost ( $p=0.53$ ) with overlap of the CIs in all time periods. The mean insulin dose is still the lowest in period 2. The percentage of patients requiring an insulin dose of  $>2$  u/kg/d (indicating insulin resistance) varied between 0 (period 2) and a maximum of 2.9% (period 1). There were missing data for 7/77 patients in period 1, 8/112 patients in period 2, 6/135 patients in period 3 and 1/139 patients in period 4.





**Figure 7: Insulin dose/day per time period (all patients)**



**Figure 8: Insulin dose/day per time period (patients captured in all 4 time periods)**

## 7.6 COMPLICATIONS

Table 7 gives an overview of the prevalence of complications during the various time periods. These could not be compared statistically, because the number of patients with documented complications in the various periods was small. The presence of retinopathy, all non-proliferative, was only documented in the last 2 time periods. One patient's type of retinopathy was unknown. Only 1 case of neuropathy was diagnosed in period 4. The UAC ratio was documented fairly consistently over all 4 time periods. It varied little over time (figure 9).

During the first time period, LJM was either not present (which is less likely) or not assessed (table 7). Similarly, only 1 patient had a documented lipogram in

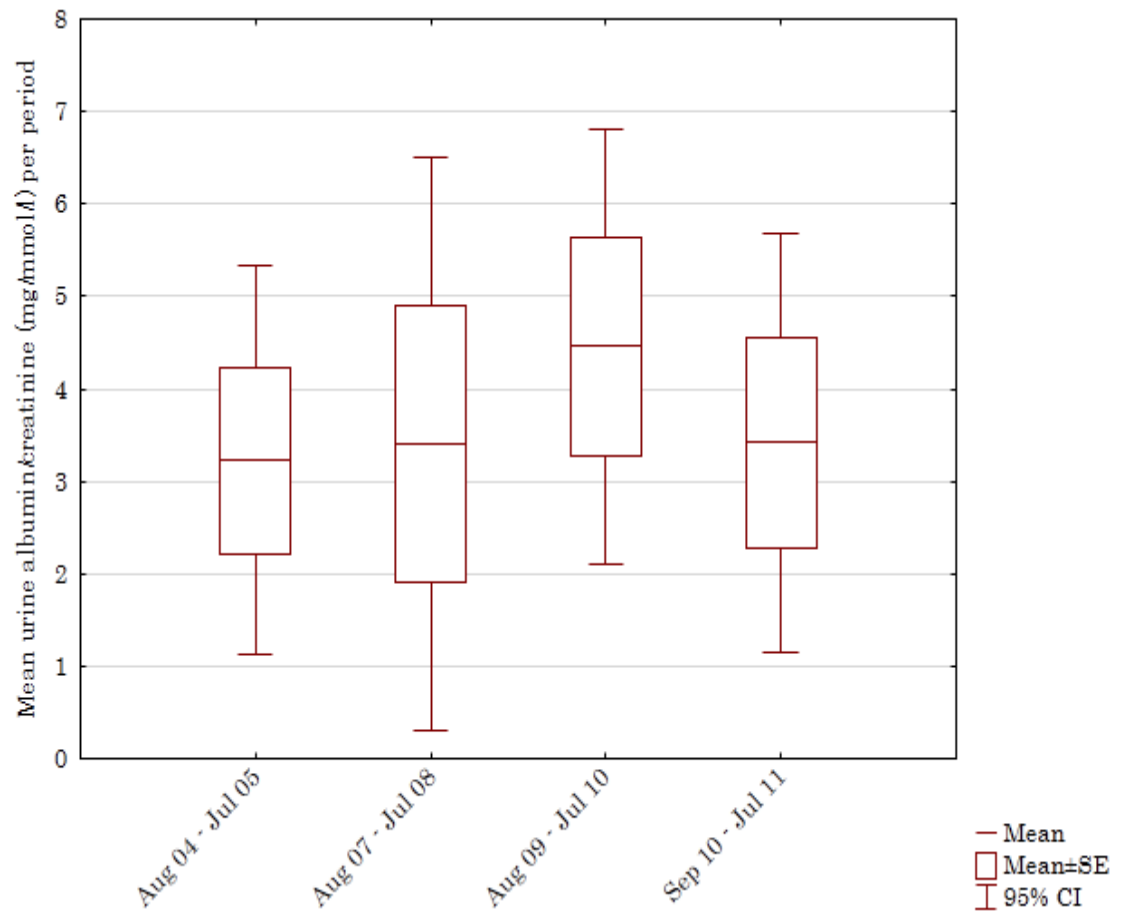
period 1. Hence it was not possible to include the lipid profiles for this period in any statistical analysis. TSC and LDLC followed a similar pattern (figures 10 and 11), both being lower in periods 3 and 4 compared to period 2, but LDLC being significantly lower (figure 11). There was a trend for HDLC to be lower in period 4 (figure 12). The TG levels were similar throughout all 3 time periods (figure 13). The majority of patients had desirable/ideal levels of TSC, TG, LDLC and HDLC except during period 2 when only 15.8 % of patients had an ideal LDLC level (table 8). The highest proportion of ideal HDLC levels of 68.2% was seen in period 2 (table 8).

**Table 7: Complications**

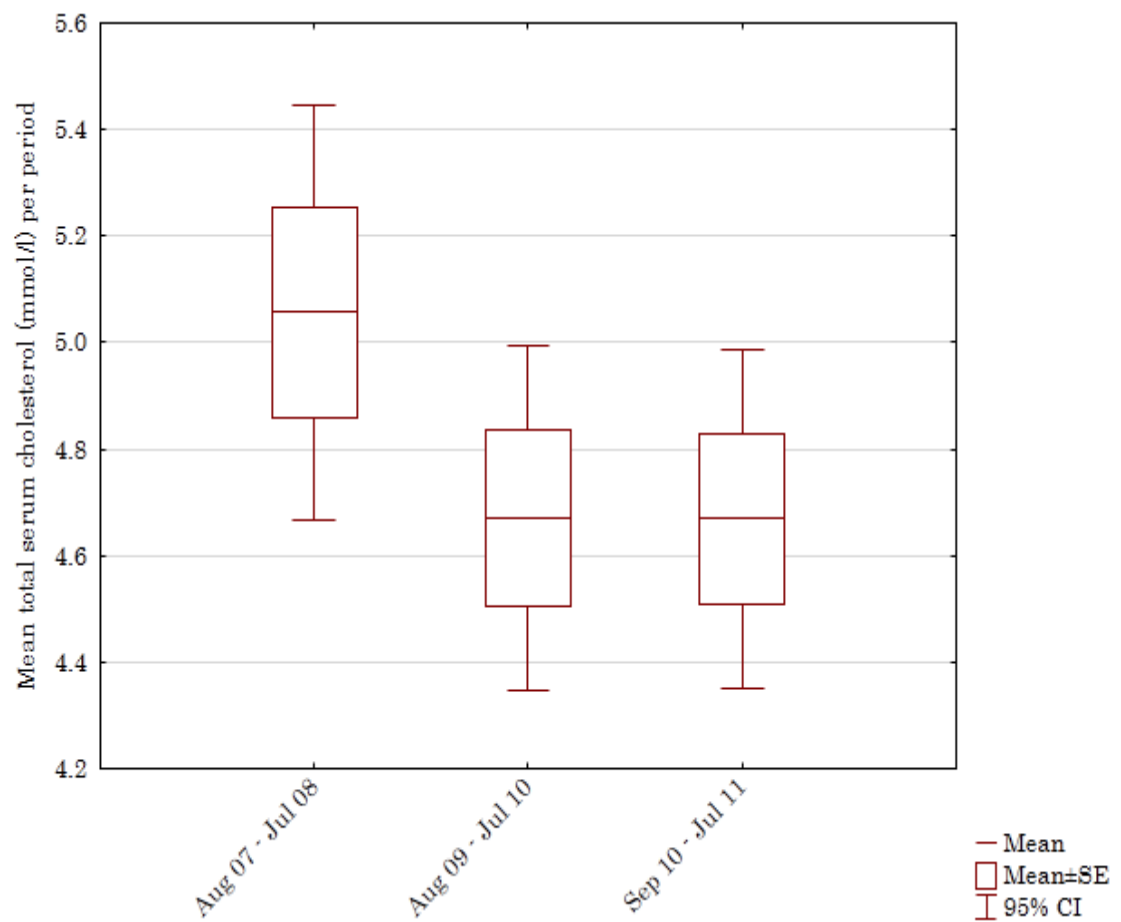
	Aug 2004- July 2005	Aug 2007- July 2008	Aug 2009- July 2010	Sept 2010-July 2011
	n (%)	n (%)	n (%)	n (%)
Microalbuminuria <sup>13</sup>	8/22 <sup>14</sup> (36.4)	7/25 (28)	30/65 (46.2)	18/67 (26.9)
Retinopathy	0/25	0/34	6/45 (13.3)	6/58 (10.3)
Neuropathy	0/26	0/39	0/79	1/88 (1.1)
Limited Joint Mobility	Not assessed	13/50 (26)	36/89 (40.4)	42/98 (42.9)

<sup>13</sup> Microalbuminuria: Urine albumin to creatinine ratio  $\geq 2\text{mg/mmol}$  in at least two of three consecutive early morning urine samples [21].

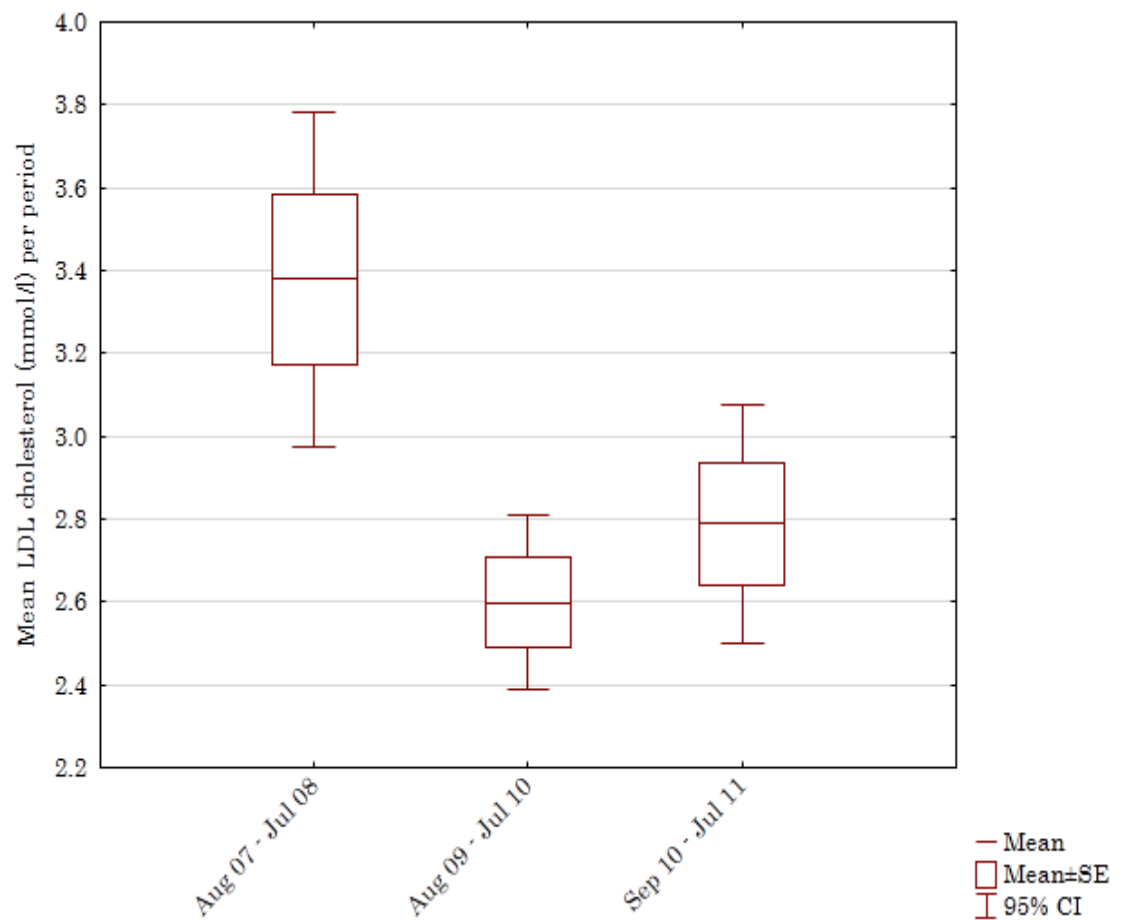
<sup>14</sup> Denominators represent the total number of patients assessed for complications in the specific time periods.



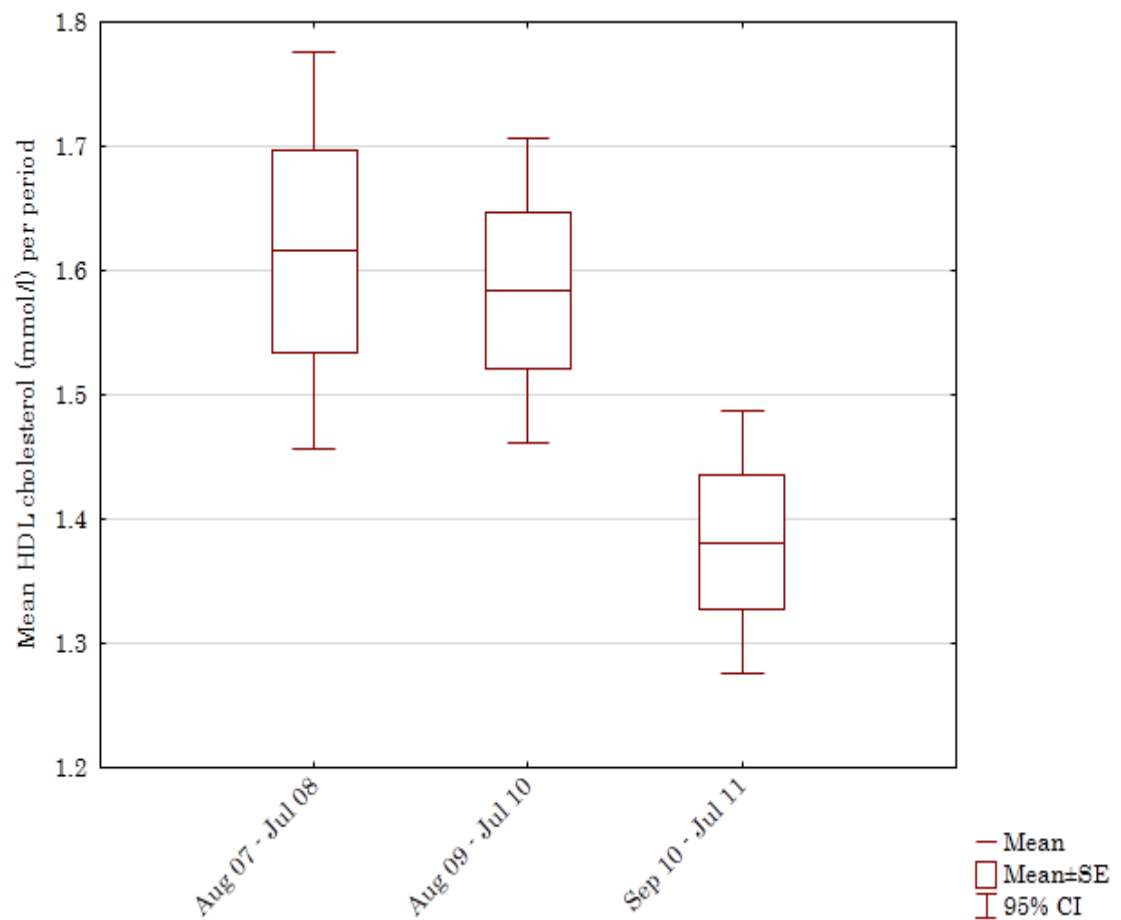
**Figure 9: Urine albumin/creatinine ratio per time period (all patients)**



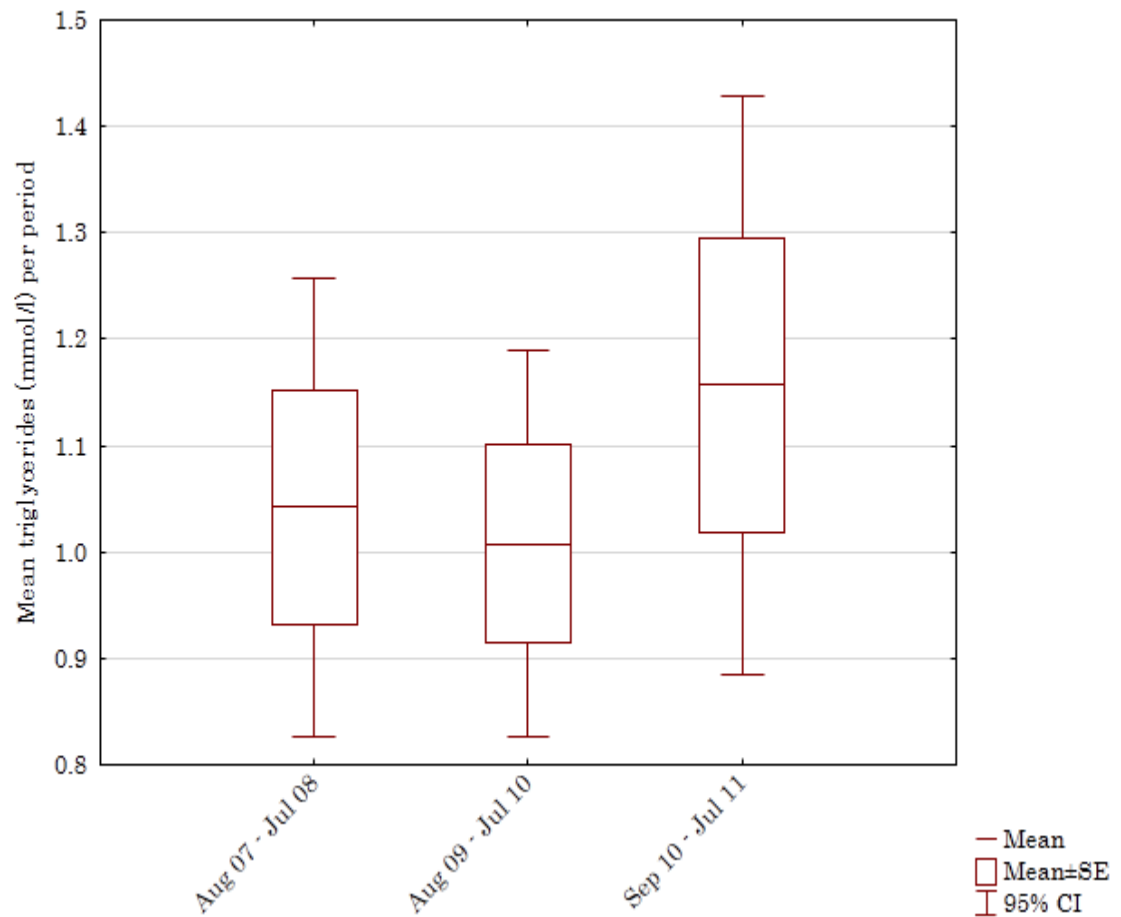
**Figure 10: Total Serum Cholesterol per time period (all patients)**



**Figure 11: LDL Cholesterol per time period (all patients)**



**Figure 12: HDL Cholesterol per time period (all patients)**



**Figure 13: Triglyceride levels per time period (all patients)**



**Table 8: Lipid profiles: Proportion of patients with ideal or poor levels<sup>15</sup>**

		Aug 2004-July 2005	Aug 2007-July 2008	Aug 2009-July 2010	Sept 2010-July 2011
		n (%)	n (%)	n (%)	n (%)
<b>TSC<sup>16</sup></b>	High	6 (17.1)	4 (13.3)	10 (15.9)	11 (17.2)
	Borderline high	3 (8.6)	10 (33.3)	6 (9.5)	6 (9.4)
	<b>Desirable</b>	26 (74.3)	16 (53.3)	47 (74.6)	47 (73.4)
<b>LDLC<sup>17</sup></b>	Very high	0	1 (5.3)	1 (1.6)	1 (2.4)
	High	1	3 (15.8)	4 (6.6)	4 (9.5)
	Borderline high	0	7 (36.8)	7 (11.5)	7 (16.7)
	<b>Near ideal</b>	0	5 (26.3)	13 (21.3)	11 (26.2)
	<b>Ideal</b>	0	3 (15.8)	36 (59)	19 (45.2)
<b>HDLC<sup>18</sup></b>	Poor	0	1 (5.3)	12 (19)	10 (23.3)
	<b>Better</b>	0	6 (31.6)	8 (12.7)	10 (23.3)
	<b>Best</b>	1 (1)	12 (63.1)	43 (68.2)	23 (53.5)
<b>TG<sup>19</sup></b>	High	0	0	4 (6.3)	5 (44)
	Borderline high	1	3 (15.8)	3 (4.7)	3 (6.8)
	<b>Desirable</b>	0	16 (84.2)	57 (89)	36 (81.8)

<sup>15</sup> Patients with missing data are not included and certain patients were seen in some time periods, but not in others.

<sup>16</sup> TSC: High: >6.2mmol/l; Borderline high: 5.2-6.2mmol/l; Desirable: <5.2mmol/l

<sup>17</sup> LDLC: Very high: >4.9mmol/l; High: 4.1-4.9mmol/l; Borderline high: 3.4-4.1mmol/l; Near ideal: 2.6-3.3mmol/l; Ideal: <2.6mmol/l

<sup>18</sup> HDLC: Poor: <1mmol/l (men); <1.3mmol/l (women); Better: 1-1.3mmol/l (men); 1.3-1.5mmol/l (women); Best: ≥1mmol/l

<sup>19</sup> TG: High: 2.3-5.6mmol/l; Borderline high: 1.7-2.2mmol/l; Desirable: <1.7mmol/l [38]

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## 8 DISCUSSION

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### 8.1 GLYCAEMIC CONTROL

The HbA1c levels initially increased from period 1 to period 2 (figure 1). The increased HbA1c levels during period 2 (when a DMT was introduced), could be explained by the fact that there was no specialist for 4 ½ months and only a part-time specialist for another 3 ½ months prior to period 2 in 2006. The paediatric diabetic service during that time was therefore managed by inexperienced staff with limited training in diabetes care. The mean HbA1c levels then gradually dropped over periods 3 and 4 with narrowing of the CIs, demonstrating tighter glycaemic control after the appointment of the DNEs (less variation with fewer outliers). In addition institutionalisation of certain patients for lengthy periods for social and psychological issues may have contributed to better control. HbA1c levels corrected to previous levels 2 years after a DNE was appointed. Considering that most of these patients [10 of the 11 girls (90.9%) and 7 of the 11 boys (63.6%)] were in the difficult adolescent phase with co-existing insulin resistance, the better glycaemic control with far less variation is a remarkable achievement. The similar HbA1c in period 1 could be explained by the fact that of the total of 22 patients, 2 patients required daily insulin doses  $\leq 0.5\text{U/kg}$ , and 8 patients were treated for less than 18 months, therefore both groups presumed to be in the honeymoon phase. One would however have expected the patients in the honeymoon phase to have an HbA1c < 7% which these patients did not. Nevertheless, these patients were captured in the relatively early stage of their disease where one would also expect a lower HbA1c. The CI was wider than in period 4, indicating that a few patients in period 1 were definitely poorer controlled than in period 4. One can only assume that the impact of the DNE and the DMT on metabolic control would be even greater as time progresses. However, it would be more difficult to bring about a further change in HbA1c the closer one approaches the target level of 7.5%.

Although there was significant improvement in HbA1c over time, only 18.8% of patients in period 1 and 10.7% of patients in period 4 (table 3) achieved HbA1c levels <7.5%, which is considered good control as per the recommended ISPAD guidelines [7, 8, 13]. Even International studies revealed that the recommended HbA1c level is seldom reached, due to numerous factors including patient-related and/or treatment-related factors (see below). Results of a study done by E.-M.Gerstl et al in 2008 in Germany and Austria found the mean HbA1c level to be 7.8% which is still slightly higher than the recommended level as per the ISPAD guidelines(2000) but lower than that of various other studies including the Hvidore study (8.3%). The mean HbA1c level of 9.7 (figure 1) achieved in our clinic overall does however compare to studies from Denmark (9.1%) and France (9.0%) [2].

Recent studies performed in African countries also demonstrated poorer glycaemic control in a high percentage of patients [5, 14, 24]. A study done by L.J Mukama et al in Tanzania in 2013 showed that only 5% of children and adolescents aged 3-19 years had HbA1c levels of 7.5%, with 44% of patients having HbA1c levels >12.5%. Their level of good glycaemic control was found to be much lower compared to our study. 36% of their patients reported omission of insulin. Longer diabetes duration and a higher insulin dose/kg were associated with increased HbA1c levels. This was found despite the appointment of 2 paediatric endocrinologists, regular clinic attendance, diabetes education, provision of glucose testing materials and provision of insulin. However, there were many limiting factors which could explain the poor HbA1c levels, including poor infrastructure, no home refrigeration for insulin storage, short period of study (6 months) and glucose testing only once per week. Mean Hba1c levels however improved slightly from 12.4% to 11.2% over 6 months; although not statistically significant [5], and still higher than our mean HbA1c of 9.7%. Results of a study performed in Rwanda in 2012 in children, adolescents and adults aged <26 years, demonstrated mean HbA1c levels of  $11.2 \pm 2.7\%$  [14, 24]. With a follow-up study, Hba1c levels were assessed at 1 year and 2 year follow-up visits, where HbA1c was found to be  $10.2 \pm 2.6\%$  and  $9.8 \pm 2.6\%$  respectively. This improvement was attributed to the establishment of regular diabetic care, HbA1c testing and increased patient education [24] and compares well to our mean HbA1c of 9.7%.

The SEARCH for Diabetes in Youth study by R.A. Bell et al in 2009, demonstrated a higher prevalence of aHbA1c level of >9.5% in children > 15 years (21.5%), compared to the younger age groups (3.4-11.2%) [39]. The

study by E.-M. Gerstl et al mentioned above also demonstrates an increase in HbA1c levels with age especially in the adolescent population. There is also a significant association of poorer glycaemic control in females compared to males due to the known differences in glucose metabolism. The increased HbA1c levels in adolescents are due to the lower insulin sensitivity and higher insulin clearance compared to younger children, associated with the growth hormone concentration. Also, because of behavioural changes during puberty, there is an increased risk of non-compliance to diabetic treatment, resulting in poorer glycaemic control [2]. In our study, there were roughly six years between period 1 and period 4. Contrary to expectations, a similar increase in HbA1c over time was not seen in our patients (figure 1). This highlights the effectiveness of the intervention.

## 7.2 DKA

The DKA rate showed improvement over time while the rDKA rate dropped drastically after period 1, but then remained static (tables 4 and 5). Credit should be given to the DMT including the DNEs. Longer hospitalisation of patients (table 6) to address social and behavioural issues would have contributed to the success. Factors outside the control of the DMT, e.g. social and psychological issues, could account for the lack of a further drop in the rDKA rate. In all time periods, more girls presented with rDKA than boys, presumably because emotional factors have a greater impact in females than in males. Girls also more frequently try to escape dangerous situations, such as sexual, physical or emotional abuse and therefore omit insulin to precipitate an episode of DKA. Similar observations were made by M. Fritsch et al [36], E. Bismuth et al [40] and A. Rewers et al [41], who cited female gender [36, 40, 41], associated psychiatric disorder [40, 41], underinsurance [40, 41] and a migrational background in patients [36] as associated factors. In the current study, there are limitations with regards to the DKA and rDKA rates. As previously explained, all DKAs may not have been documented because patients residing in rural areas may have been managed at rural hospitals because of the long travel time and minimal resources available for transport to tertiary hospitals. Teenagers may have also presented to the adult unit to be managed without redirection to the paediatric and adolescent diabetic unit at TCH.

Our DKA rate is appallingly high (23.5/100 patient years) compared to other studies. The DKA rate was found to be 7.5/100 patient years by the DCCT in adolescent patients [37]; 8/100 patient years in a Denver study by A Rewers et al (2002) in both children and adolescents [41]; 6.3/100 patient years in a German and Austrian study by M Fritsch and J Rosenbauer et al (2011) in both children and adolescents [36]; and 14.8% in a Tanzanian study by L.J. Mukama and A Nyindo et al (2013) in children and adolescents 3-19 years of age. DKA risk in the Tanzanian study was associated with insulin omission ( $p < 0.05$ ), higher HbA1c levels, higher prescribed insulin dose and as with other studies, adolescent age and female gender. The DKA rate in the Tanzanian study is lower than in our study and has been attributed to the greater availability of insulin during the study's 6 month period [5]. Even the rDKA rate in our study is unacceptably high (9.6% in period 4). In Rewers's study, the incidence was only 4.9% (61/1243) with 55.7% (34/61) being female ( $p = 0.03$ ) [41]. The incidence in M. Fritsch's study was even as low as 1% [36].

### **8.3 NUMBER OF ADMISSIONS, LENGTH OF HOSPITAL STAY AND NUMBER OF CLINIC ATTENDANCES**

#### **Number of admissions**

The study demonstrates that there was a steady decline in the number of admissions. This was true for the whole patient population, but even more pronounced for patients being followed through all 4 periods (figures 2 and 3). For the latter group this was highly statistically significant ( $p = 0.00127$ ), with no overlap of confidence intervals of periods 1 and 4 (95% CI 0.46-1.12 and 0.02-0.34 respectively). The number of admissions dropped by about 25 % (from a mean of 0.7 to 0.5 admissions/period) for the whole patient population (figure 2) and by 75 % (from a mean of 0.8 to 0.2 admissions/period) for patients being followed through all periods (figure 3). This attests to the effectiveness of the full DMT and constitutes a cost saving for the hospital. It mirrors the change seen in the HbA1c. A study done by F.J. Cowan et al at the University Hospital of Wales, also demonstrated a reduction in admission rates from 100% before implementation of a DNE to 41.7% in the year after implementation of the DNE [9].

### **Length of hospital stay**

There seems to be a trend for keeping diabetic children in hospital for a shorter duration and providing most of the care on an outpatient basis. For example, the length of hospital stay in the newly diagnosed type 1 diabetics in F.J. Cowan's study was reduced, from a median hospital stay at diagnosis of 5 days to 1 day, 1 year after implementation of a DNE [9]. This is however only possible if the service provided is of a high standard, community based, and social circumstances are favourable. Our patient population however has to rely on hospital services far more frequently, because 25% reside in rural areas, do not have access to transport and have poor financial circumstances. Hence regular visits to the clinic for training are impractical. DNEs are also not available in the periphery. Length of admission in our unit is therefore generally longer than in other units.

Compared to period 1, hospital stay in our patient population was longer during periods 2-4 for several reasons. Firstly, patients were hospitalised for longer periods in an attempt to improve glycaemic control by facilitating training of all caregivers involved in the care of each respective child (who often had to come from far). Secondly, patients from unstable home environments often had to await alternative placement. Others had to rely on hospital transport as they resided in rural areas, did not have the financial means and could not reach home otherwise. Despite this, the number of patients hospitalised for > 30 days decreased progressively, presumably implying that some of these factors could be addressed by the full DMT more efficiently.

### **Number of clinic attendances**

Most patients attended the diabetes clinic approximately 4 times a year (figure 4). This conforms to the recommended minimum annual number of clinic attendances. Periods 2 and 3 however differ significantly from each other. The mean clinic attendance/period was 3.9 (95% CI 3.44-4.34) in period 2 and 4.9 (95% CI 4.4-5.4) in period 3. This constitutes a 25% increase in attendance rates between periods. Clinic attendance in period 2 is the worst of all, presumably because it immediately follows the 4 ½ month period where inadequately trained medical officers were responsible for the care of patients. It corresponds to the period where the HbA1c was the highest (figure 1), indicating suboptimal care. Once tighter control was achieved, clinic

attendance could be allowed to drop in period 4 (figure 4) without a deterioration of HbA1c levels. Glycaemic control in fact continued to improve (figure 1).

The non-attendance rate at the outpatient clinic documented by F.J. Cowan et al at the University Hospital of Wales was also significantly reduced from 19% to 10% in the children's clinic (<14 years of age) and from 38% to 23% in the adolescent clinic (>14 years of age), 1 year after implementation of a DNE [9]. Although similar, the findings of our study are not quite comparable to the study above, because we analysed attendance rather than non-attendance rate.

## 8.4 INSULIN THERAPY

### **Number of insulin injections per day**

Both the DCCT and its follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC) trial, confirms that intensified insulin therapy ( $\geq 3$  insulin injections/day or continuous insulin pump therapy) in type 1 diabetic paediatric patients, improve long-term glycaemic control compared to conventional insulin therapy (1-2 insulin injections/day) and therefore reduce the incidence of complications as well as delay progression of existing complications [42, 43, 44]. The DCCT demonstrated a mean HbA1c level at the end of their 10 year study period of 7.2% with intensive insulin therapy versus a mean HbA1c level of 9.1% in the patients treated with conventional insulin therapy in their study population of both adults and adolescents. With the follow up study Epidemiology of Diabetes Interventions and Complications Study (EDIC), HbA1c levels were found to be 8% in both intensive insulin therapy and conventional insulin therapy groups, 18 years after completion of the DCCT study [43].

Our study did not compare the effect of intensive insulin therapy versus conventional insulin therapy on glycaemic control. With time however, there was a significant increase in the number of patients receiving intensive insulin therapy (basal bolus regimen). The dedicated DNE could facilitate such a change, as this time and labour intensive regimen requires considerably more education and counselling.



Many of the patients in our study population were on the modified conventional insulin regimen (3 insulin injections/day) throughout the 4 time periods as chosen by the patients and parents themselves. This is due to the fact that many of our patients and parents lack the capacity or financial resources to comply with the basal bolus regimen. Patients initially on the conventional regimen (2 insulin injections/day) were switched to the modified conventional regimen, possibly contributing to the overall better glycaemic control.

### **Insulin dose per day**

The highly significant difference in daily insulin dose between period 1 and periods 2-4 can probably be attributed to a different management approach by the two different endocrinologists employed by the hospital (figure 7). The HbA1C levels achieved in periods 1 and 4 were similar, implying that there was less insulin wastage with a consequent cost saving for the hospital.

## **8.5 COMPLICATIONS**

The assessment of complications is initiated 5 years after onset of T1DM in pre-pubertal patients versus 2 years in pubertal patients. As an aide memoire a diabetes complication chart was introduced in the diabetes clinic during period 2.

### **Microalbuminuria**

The prevalence of microalbuminuria for all patients was variable for the various time periods with period 4 having the lowest prevalence i.e. 26.9% (table 7). No statistical test could be done for the whole population as it was not a stable population i.e. patients were entering and exiting the cohort in each period. Following the same patients throughout all 4 time periods however, revealed a similar mean UAC ratio in all periods. For prevalence of microalbuminuria to therefore truly change, a longer period of observation after intervention is probably needed.



A study by Kiemans Raile et al published in 2007, demonstrated the prevalence of persistent microalbuminuria to be 25.4% which is similar to our findings. However, this study included children, adolescents and adults and was within 40 years of diabetes duration [20]. In the MIDAC study of 2000 performed in paediatric diabetic outpatient clinics in the United Kingdom and Republic of Ireland, only 9.7% of 10-20 year old patients had microalbuminuria [21]. The Rwandan study by S.L. Marshall et al in 2013, had microalbuminuria and nephropathy rates of 20.8% and 4.7% respectively, which is also quite similar to our rates. However, not all patients in the Rwandan study were screened for complications because of logistical problems, so the rates may actually be higher. Patients with microalbuminuria compared to those without, had a younger mean age at diagnosis ( $17.9 \pm 4.2$  years vs.  $18.9 \pm 4.3\%$ ,  $p=0.01$ ) and longer duration of diabetes ( $5.0 \pm 3.1$  years vs.  $3.5 \pm 3.2$  years,  $p=0.02$ ). HbA1c was not found to be statistically significantly different ( $p=0.16$ ) [14]. At the 1 and 2 year follow-up visits, the prevalence of microalbuminuria (21.0% vs. 18.8% vs. 19.6%), or nephropathy (4.7% vs. 7.8% vs 5.4%) did not significantly change [24].

The DCCT demonstrated that with intensive insulin therapy, the development and progression of microalbuminuria was reduced by 39-54% in patients 13-39 years of age [44, 45, 46]. A similar reduction of microalbuminuria prevalence of 58% was seen in our total patient population once all patients were treated on a minimum of 3 insulin injections per day.

### **Retinopathy**

During periods 1 and 2, no children with retinopathy were diagnosed. Whether all the children who qualified for screening actually attended their ophthalmology clinic appointments is not known. Circumstantial evidence suggests that attendance at that clinic was poor. During period 4, the policy was therefore changed and retinal photography was performed on the day the children attended the diabetes clinic. This is the most likely explanation for why most patients were screened during this time period ( $n=58$ ). The prevalence of retinopathy in period 3 and 4 are comparable (13.3% vs. 10.3%). This is slightly lower than the prevalence of mild non-proliferative retinopathy of 16.3% [17] found by R.W. Holl in a German study of paediatric and adolescent type 1 diabetics.

## **Neuropathy**

Only 1 patient in period 4 was found to have peripheral neuropathy. How neuropathy was excluded in period 1 is not known. Screening for vibration sense was only introduced late in period 3. Presumably neuropathy was not always excluded and therefore frequently missed.

Studies from Australia indeed suggest that as a complication of diabetes, peripheral neuropathy should be more common than retinopathy. A cohort study done by F. Mohsin et al for example even demonstrated an increase in peripheral nerve abnormalities from 12% to 24% between 1990 and 2002 in adolescents aged 12-20 years [15]. E. Downie et al assessing adolescents aged 12-20 years, also demonstrated an increase in prevalence of peripheral nerve abnormalities from 7% to 14% between 1990 and 1999. This remained static at 14% until 2009 [23]. The Rwandan study by S.L. Marshall et al in 2013 demonstrated a neuropathy rate of 21%, which was significantly associated with a higher mean age compared to those without neuropathy ( $23.0 \pm 1.6$  years vs.  $18.6 \pm 4.2$  years,  $p=0.02$ ) [14].

## **Limited joint mobility**

During period 1, LJM was never documented and therefore probably not routinely assessed. As the diabetes complication chart was introduced in the clinic, more patients were recognized with this complication, explaining the progressive increase in prevalence of LJM from 26% in period 2 to 42.9% in period 4.

The prevalence of LJM, as established by the prayer manoeuvre (test to oppose palmar surfaces at the interphalangeal or metacarpophalangeal joints), varies significantly between studies: 7% in C. F. Clarke's group from Australia (patients 8.6-18.5 years of age) [28], 26% in S. K. Garg's group from the USA (patients more than 14 years of age) [32], 36.5% in L. Kennedy's group from Belfast (patients 5-57 years of age) [30], 42% in J. E. H. Brice's group from Nottingham (patients 2-16 years of age) [31], and 65.1% in E. Montaña's group from Barcelona (patients more than 18 years of age) [29]. The prevalence found in our study is thus what would be expected from the literature.

Studies by Montana and Clark suggest that LJM may precede microangiopathy in adults and adolescents, making it a useful marker for the risk of developing microvascular complications such as microalbuminuria and retinopathy [29, 30, 32]. LJM was found in 90.0% of adult T1DM patients with microalbuminuria compared to only 57.4% of patients who had a normal urinary albumin excretion rate. In patients with retinopathy, joint mobility was more severely impaired and duration of diabetes was longer, compared to patients without retinopathy [29].

S. K. Garg also demonstrated an association of LJM with glycaemic control. The mean HbA1c level was higher (12.47% versus 11.73%) in patients 14-34 years of age with LJM than those without ( $p=0.0014$ ) [32]. It was however not the aim of our study to look for associations between LJM and HbA1c, microalbuminuria or retinopathy. These analyses however could still be performed at a later stage.

### **Lipid profiles**

The significant decrease of LDLC in period 3 (figure 11) is most likely the result of improved insulin therapy and better dietary control. The associated drop in HDLC is however of concern (figure 12). As this is the period with better glycaemic control, presumably diabetes itself is unlikely to account for this decrease. Instead it might be due to lack of physical activity. Data on physical activity was however not obtained. BMIs were also not recorded during the study. We can only assume that the wider use of new technologies which were introduced in South Africa at the time, could inter alia have led to a more sedentary lifestyle.

The overall prevalence of abnormal lipid profiles was as follows: borderline high/high TSC (TSC >5.2mmol/l) 29.9%, borderline high/ high/ very high LDLC (LDLC >3.4mmol/l) 28.7%, poor HDLC (HDLC <1mmol/l) 18.4% and borderline high/high TG concentration (TG >1.7mmol/l) 14.1%. The data suggests that our patient population has a much higher prevalence of abnormal lipid profiles than the SEARCH for Diabetes in Youth Study [27] as well as the study by Marcovecchio and Associates [25].

The SEARCH for Diabetes in Youth Study demonstrates that 19% of type 1 diabetics 10-22years of age have a TSC >5.2mmol/l, 15% have a

LDLC>3.4mmol/l, 12% have a HDLC<1mmol/l and 10% have a TG concentration >1.7mmol/l. This study does however have its limitations in that the participants were not a random sample and the rate of participants in the study was low especially amongst the older youth, possibly leading to an underestimation of dyslipidaemia [27].

Marcovecchio and Associates found a high prevalence of lipid abnormalities in their adolescent type 1 diabetic population (10-16 years of age). TSC>5.2mmol/l during follow-up was found to be 18.6%, 9.6% of the population had a high LDLC>3.4mmol/l, with HDLC<0.9mmol/l being only 2.5% and TG concentration>1.7mmol/l being 20.1% of the population. Influencing factors on lipid abnormalities were found to be age and duration of diabetes ( $p<0.001$ ). HbA1C was associated with all the abnormal lipid concentrations except HDLC ( $P<0.001$ ), and BMI was associated with all the abnormal lipid concentrations except TSC ( $P<0.05$ ) [25]. As with LJM, it was not the objective of the current study to look for any of these associations.

A study performed by I Sylvester at Muhimbili National Hospital in Dar es Salaam in 2012, found a high TSC and LDLC of 25.5% and 29.6% respectively which is comparable to our study. Low HDLC and elevated TG concentrations of 13.3% and 5.1% were however not comparable to our study [26].

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## 9 CONCLUSION AND RECOMMENDATIONS

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Diabetes care deteriorated after inexperienced personnel took over the management of diabetes patients at the Tygerberg Children's Hospital. The care improved again after a paediatric endocrine specialist was re-employed and a DMT was implemented. It improved further after the appointment of a DNE. The following changes were observed:

1. HbA1c decreased and showed less variation.
2. DKA and rDKA rates were reduced.
3. The number of admissions steadily decreased.
4. The length of hospital stay initially increased for some patients as social and psychological issues of the patients were more readily identified. As these were addressed, the proportion of patients staying longer than a month reduced again.
5. The number of insulin injections/day increased. More specifically the proportion of patients on the basal bolus regimen (intensive insulin regimen increased from 2.8% to 17.5%.
6. Complications were more readily identified but the prevalence of the various complications was not reduced.
7. The clinic attendance rate initially improved in an attempt to correct poor glycaemic control. Once this had been achieved the attendance rate dropped, but remained  $\geq 4$  recommended annual visits in more than half the patients.

This suggests that a multi-disciplinary approach to the management of diabetes plays a big role in the improved outcomes of paediatric diabetic patients.

It is therefore recommended that inexperienced personnel should not be entrusted with the care of diabetes patients. For optimal care, the full DMT should

continue to perform its vital function. In particular, the service of the DNE is invaluable and every effort should be made to retain her position.

This study should be repeated after another 2 years to assess ongoing improvement of all parameters. As a quality control assessment, the study should also be repeated after every new DNE has been working for a year.

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